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Annotations

Bone marrow transplantation for leukaemia

Over 10 years have passed since the classic paper from Seattle showed that a small proportion of patients with end stage leukaemia could be cured by total body irradiation, cyclophosphamide, and infusion of bone marrow from an HLA identical sibling donor.[1] Since that time bone marrow transplantation has become safer and more widely available, and thanks to relentless media interest forms the subject of endless enquiries from parents and relatives. Yet the decision to perform bone marrow transplantation, particularly in first remission of acute leukaemia, is a difficult one and involves careful assessment of the possible risks and benefits This annotation will focus on the present indications for bone marrow transplantation in leukaemia and the expected results, but some appreciation of the possible complications is essential. The indications will, of course, change in the future as more effective chemotherapy regimens develop or bone marrow transplantation, or both, become safer

Risks and complications of bone marrow transplantation

The most widely used preparative regimens for bone marrow transplantation involve high doses of cyclophosphamide and fractionated or unfractionated total body irradiation. This treatment causes profound myelosuppression for at least two to four weeks and long term immunosuppression. The infective risks associated with bone marrow transplantation have been extensively reviewed and include both bacterial and fungal sepsis.[2] Cytomegalovirus infection may cause pneumonitis and long term immunosuppression exacerbated by graft versus host disease may predispose to pneumococcal infection. Allogeneic bone marrow transplantation with a sibling donor who is HLA identical carries a significant risk of graft versus host disease and measures to prevent this complication either by treatment of the recipient, or the donor bone marrow, are essential [3]

Despite these problems bone marrow transplantation is in general well tolerated by a fit child in remission and perhaps the main concern for the paediatrician lies in the late effects of treatment. Assessment of growth and endocrine function in children who have received total body irradiation and cyclophosphamide shows gonadal failure, thyroid dysfunction, spinal shortening, and particularly in those who have received previous cranial irradiation, abnormal hypothalamic-pituitary function and learning problems.[4 5] Many of these late effects are attributable to total body irradiation. There are alternative preparative regimens using chemotherapy alone such as the combination of busulphan and cyclophosphamide,[6 7] but both the efficacy and late toxicity of such treatment have been less well studied

Choice of a donor

A major limitation to the use of bone marrow transplantation is that only about one in three children in the United Kingdom will have an HLA identical sibling donor Transplantation from a non-identical family member increases the risk of graft versus host disease and failure of engraftment.[8] There are now reports of the successful use of matched unrelated donors in chronic leukaemia but the search for these is time consuming and expensive.[9]

Autologous marrow transplantation is less hazardous than allogeneic transplantation, and in theory more freely available, but carries a higher risk of relapse which may be due to the reinfusion of leukaemic cells or the loss of any graft versus leukaemia effect. Despite these considerations it is unclear at present whether attempts to purge the marrow of possible residual leukaemic cells are necessary [10]

Chronic myeloproliferative disease

Chronic myeloid leukaemia in childhood resembles the disease in adults with a median survival of three to four years. Two transplant groups have reported actuarial survival of 49%[11] and 72%[12] after bone marrow transplantation from sibling donors, the latter report had a median follow-up time of two years Successful bone marrow transplantation has also been reported in juvenile chronic myeloid leukaemia and the monosomy 7 syndrome.[13 14] Allogeneic bone marrow transplantation is the treatment of choice for these rare disorders and, in patients where no sibling donor is available and the pace of the disease permits, a search for a matched unrelated donor seems appropriate.[illegible]

Acute myeloid leukaemia

Advances in the treatment of acute myeloid leukaemia have been recently reviewed and children have been among the major beneficiaries.[15] The outlook for paediatric acute myeloid leukaemia has improved from the previous appalling 12% event free survival rate both for children receiving bone marrow transplantation and those treated with chemotherapy alone.[16] With modern intensive chemotherapy and full supportive care over 85% of children with acute myeloid leukaemia should achieve remission. The best overall results from chemotherapy protocols have been in unrandomised, often single centre studies with event free survival of 30–40%.[17–19] Survival rates in small series of children with acute myeloid leukaemia from the time of marrow transplantation in first remission are in the order of 65%.[20 21]

The failures in the chemotherapy reports are largely due to relapse, and those in the series of bone marrow transplantation due to transplant related deaths. There is a continuing debate, reviewed elsewhere,[15] between the proponents of bone marrow transplantation in first remission for children with acute myeloid leukaemia and a donor, and chemotherapy with bone marrow transplantation at the first sign of relapse. All published studies directly comparing bone marrow transplantation and chemotherapy in first remission favour the former,[22–25] however, and at present it must be the preferred option for children with acute myeloid leukaemia who have a donor.

There is great interest in the use of autologous bone marrow transplantation as a form of intensive treatment in first remission. This approach has been pioneered in adults with acute myeloid leukaemia, using regimens with and without total body irradiation.[26] The results of the reported uncontrolled studies are encouraging but open to the criticism that the patients are a selected group who have survived past the risk of early relapse. The new Medical Research Council trial for children and adults with acute myeloid leukaemia (AML 10) will address this important question and starts this spring. All patients will receive intensive induction and consolidation and those with an HLA identical sibling donor will be eligible for allogeneic bone marrow transplantation. All those without a donor will undergo marrow harvest and storage and will then be randomised to receive chemoradiotherapy and autologous marrow transplantation or no further treatment. Patients relapsing after chemotherapy alone will be eligible for autologous marrow transplantation in second remission.

Lymphoblastic leukaemia

The prognosis of children with acute lymphoblastic leukaemia who relapse during treatment remains poor.[27] Long remissions may be obtained in children relapsing after elective cessation of treatment or even, according to one recent report, relapsing more than 18 months from diagnosis.[28] In our experience, after long term follow up, however, many such patients may still eventually again relapse.[27] Actuarial disease free survival in children receiving allogeneic transplantation in second remission is reported as ranging from 27–40%[29–32]; the major cause of treatment failure is further leukaemic relapse. A much higher survival rate of an estimated 64% at five years has recently been reported in children prepared for transplant with hyperfractionated total body irradiation preceding cyclophosphamide.[33]

While there is no doubt that children with acute lymphoblastic leukaemia who relapse during treatment, and probably off treatment as well, should be offered a transplant if they have a compatible sibling donor, in our experience the impact of such a programme has been small because of the small number of children with donors and the instability of second remission in many children.[34] A recent report showed a disease free survival rate of 20% in patients with relapsed acute lymphoblastic leukaemia after autologous transplantation,[32] and the time seems ripe for a trial comparing autologous bone marrow transplantation with chemotherapy in children with acute lymphoblastic leukaemia in second marrow remission.

Isolated central nervous system relapse has a poor prognosis[35 36] and bone marrow transplantation should be considered in suitable patients and in those with an overt testicular relapse during treatment.[37] Boys with testicular relapse after treatment has been stopped are curable by conventional chemotherapy and radiotherapy.[27] The most controversial area lies in the selection of children with acute lymphoblastic leukaemia for bone marrow transplantation in first remission. There are a small number of children with an unquestionably poor prognosis, for example those in whom the leukaemia is associated with certain cytogenetic abnormalities for whom such treatment is justified on an uncontrolled basis.[38] For others, such as children with a very high initial leukocyte count, bone marrow transplantation should be investigated in the context of a clinical trial. In the present Medical Research Council UKALL X trial allogeneic transplantation may be offered to children with a presenting leukocyte count of greater than 100×10^9/l who have a compatible sibling. It is thus hoped to obtain a comparison with the outcome of children receiving intensive chemotherapy

Conclusion

Chemoradiotherapy and transfusion of allogeneic or autologous marrow is the most intensive short term treatment available for childhood leukaemia. It is becoming increasingly available as regional transplant units open in the United Kingdom. Paediatricians have an excellent record of collaboration in treatment of childhood leukaemia and it is essential that this collaboration is extended to include critical evaluation of bone marrow transplantation as a form of treatment.

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Mitochondrial DNA and genetic disease

Mitochondrial DNA (mtDNA) became news a few months ago when a publication in *Nature* announced that we may all be descended from a single African woman who lived 200 000 years ago.[1] The 'mitochondrial African Eve' hypothesis is based on the fact that mitochondria are strictly maternally inherited, and the accumulation of mutations can be used as a genetic clock.[2]

But mtDNA should not just remain the province of evolutionary biologists, feminists, and religious fundamentalists. To paediatricians it offers an explanation for maternal inheritance patterns in human disease, as an individual's mitochondria are inherited exclusively from the mother. For example, mitochondrial mutations could cause some types of mitochondrial myopathy,[3] Leber's optic neuropathy,[4] and could influence the clinical manifestations of congenital myotonic dystrophy[5] and neurofibromatosis.[6]

The mitochondrial genome: 'small is beautiful'

Mitochondria are intracellular organelles which are key elements in oxidative phosphorylation Their inner membrane binds the four complexes of the electron transport chain and adenosine triphosphate synthase (complexes I to V respectively). Mitochondria are the only source of extranuclear DNA in man, and each one contains two to 10 copies of a circular piece of DNA, which compactly encodes a minority of the RNAs and proteins the mitochondrion needs to function (figure).[7] The billions of molecules of mtDNA in an individual are usually all identical, and inherited from the mother. This is presumably because the sperm contributes almost no cytoplasm to the zygote. A disease caused by a mutation in mtDNA would therefore be maternally inherited

Characteristics to be expected of diseases caused by mitochondrial mutations

A disease caused by a mitochondrial mutation might have exclusively maternal transmission, a high proportion of offspring affected or transmitting the disease (compared with 50% in X linked disorders), and a biochemical defect in an enzyme with mitochondrially encoded subunits (The absence of the latter point does not exclude a causative mitochondrial mutation. For example, in mice the expression of a maternally transmitted antigen (MTA), is dependent on a variant mtDNA although the mechanism by which it interacts with this nuclear gene encoding the protein antigen is obscure.[8]) Likely human diseases include the mitochondrial myopathies, Leber's optic neuropathy, congenital myotonic dystrophy, and chloramphenicol induced aplastic anaemia. These criteria exclude a large number of conditions where nuclear encoded mitochondrial enzymes may be affected such as Leigh's encephalopathy, where inheritance is probably recessive.

A familiar alternative explanation for maternal inheritance is a transplacental biochemical factor, as occurs in transient neonatal myaesthenia gravis. Although this could explain the initial improvement in congenital myotonic dystrophy it does not explain the persistent developmental delay nor why non-myotonic offspring are unaffected, nor the progressive degeneration in Leber's and mitochondrial myopathy. While a biological transplacentally transmitted factor such as a slow virus could explain prolonged effects, there is no supporting epidemio-

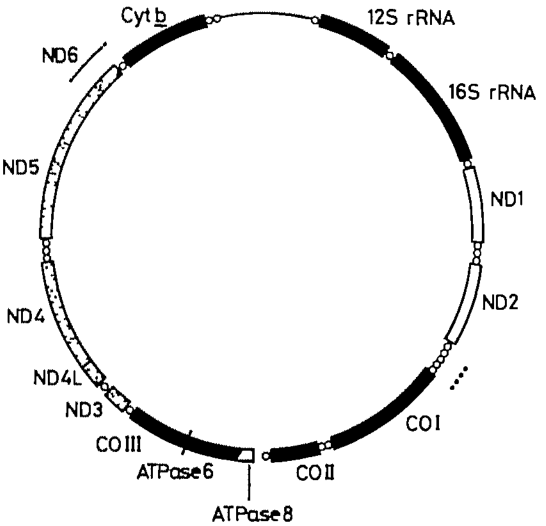

Figure *The human mitochondrial genome COI to COIII. subunits 1 to 3 of cytochrome C oxidase, ND1 to ND6, and ND4L: subunits 1 to 6 and 4L of NADH-dehydrogenase; ATPase 6 and 8 subunits 6 and 8 of* H^+ *-ATPase, Cyt b apocytochrome B, O transfer RNAs* logical nor histological evidence. Alternatively, mitochondria might malfunction because of a nuclear mutation, causing male sterility due to the high energy requirements of the sperm Finally, there is new evidence for 'imprinting' nuclear DNA according to its parent of origin.[9]

Mitochondrial myopathies

The mitochondrial myopathies are a heterogenous group of rare disorders often associated with defects in the electron transport chain They are characterised by abnormal mitochondria on muscle biopsy However, clinical manifestations are not confined to skeletal muscle. Patients may present in the neonatal period with lactic acidosis, generalised weakness, and the Fanconi syndrome[10] or later in childhood and early adult life with Kearn's Sayre syndrome,[10] myoclonic epilepsy and ragged red fibres (MERRF),[3] or mitochondrial encephalomyopathy lactic acidosis with stroke-like episodes (MELAS)[11] These clinical groups have limited nosological usefulness, however, as there is a range of disease and considerable variability even within a family.[12] Moreover, the biochemistry does not clearly parallel the clinical classification.[13] Although most cases are sporadic, maternal inheritance is frequent in familial cases,[13 14] and one large family with eight affected members has been described in which autosomal dominant and X linked inheritance was extremely improbable.[3] While there are few families in which 100% of offspring are clearly affected, subclinical involvement has been described.[3] It follows that mitochondrial mutations may well be causative in a proportion of these families.

Leber's optic neuropathy

Leber's optic neuropathy causes blindness with optic atrophy in adolescents and young adults,[15] and should not be confused with Leber's amaurosis (retinal degeneration with visual loss in infants).[16] It is exclusively maternally inherited, with a male:female ratio of 7:1 and around 80% of daughters becoming asymptomatic carriers.[4] The biochemical basis is not well established. but some studies implicate rhodanese[17] Histology occasionally shows similarities with mitochondrial myopathy.[18 19] It therefore partly fulfills the criteria for a mitochondrial disease, but if so, interactions of mitochondrial and nuclear gene products are involved (see discussion of mouse MTA above)

Congenital myotonic dystrophy

Myotonic dystrophy is an autosomal dominant condition caused by a mutation on chromosome 19.[20] Although most cases present in adult life, around 10% are symptomatic in the neonatal period with hypotonia, poor suck, respiratory problems, and mental retardation. In these cases the mother is nearly always the affected parent.[5] This could be explained by a transplacental factor. Alternatively some part of the mitochondrial genome could interact with the chromosome 19 defect, and the neonatal presentation occur only when both are present

Chloramphenicol induced asplastic anaemia

Chloramphenicol is known to inhibit mitochondrial protein synthesis and resistance is associated with a point mutation in the DNA coding for the 16s rRNA, the hypothetical binding site.[21] A mutation in the binding site might predispose to chloramphenicol induced aplastic anaemia. Although pedigrees are consistent with maternal inheritance, however, familial cases are too rare for certainty.[22 23]

Ways of looking for mitochondrial mutations

An altered mitochondrially encoded protein product, or more directly an analysis of the DNA itself could show a mitochondrial mutation. Most patients with mitochondrial myopathy appear to have normal mitochondrial proteins or a generalised reduction.[24] One case has been shown to have reduced levels of a single mitochondrially encoded peptide.[25]

Gross alterations in mtDNA can be investigated by detection of restriction fragment length polymorphisms[26]: subtle mutations such as single base changes, short insertions or deletions require DNA sequencing. So far, restriction mapping of patients with mitochondrial myopathy[27 28] and Leber's optic neuropathy[29] has not shown any such major DNA changes in DNA from white cells A recent unconfirmed report, however, suggests that there may be deletions of up to 7kb in muscle mtDNA in a proportion of patients with mitochondrial myopathy[30]

Thus far there is no published mtDNA sequence data for mitochondrial myopathy, Leber's optic neuropathy or myotonic dystrophy, although work is currently in progress. Sequence data on one patient with chloramphenicol induced aplastic anaemia shows a point mutation which could interact with chloramphenicol binding.[23] As this is present in a higher proportion of the normal population than are sensitive to chloramphenicol induced aplasia, its importance is uncertain

Conclusion

Maternally inherited diseases could be caused by mutations in the mitochondrial genome. Some of the mitochondrial myopathies are probably examples of this, and perhaps Leber's optic neuropathy and susceptibility to chloramphenicol induced aplastic anaemia. Other diseases whose phenotype is affected by the parent from whom the abnormal gene originates could be caused by an interaction of abnormal mitochondrial and nuclear gene products. Clarification of these questions will aid genetic counselling, might enable non-invasive diagnosis, and allow therapeutic possibilities.

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Phototherapy: an ocular hazard revisited

Phototherapy is an established and effective treatment for neonatal jaundice.[1] There remains concern, however, that the necessary light exposure may pose a potentially noxious stimulus to the eyes of neonates.[2–4] Recent studies have suggested that, irrespective of phototherapy, prolonged exposure to 'bright' ambient light may damage cone photoreceptors[3] and increase the incidence of retinopathy of prematurity.[5] In view of these findings it is perhaps timely to reconsider the potential ocular hazard posed by phototherapy and the practices required to minimise the likelihood of damage occurring.

The efficacy of 'patching'

The eyes of phototreated infants are routinely 'patched', because it has been shown that the intensity of light in phototherapy units can cause retinal damage in animals.[2] In a study of 12 different eyeshields obtained from neonatal units within the United Kingdom, Chin *et al*[6] found that all shields tested were extremely effective in reducing the intensity of incident light. They and others,[7] however, noted that patches are prone to slip. Such occurrences are explicable on two counts: it is often difficult to secure eyeshields effectively and, in addition, nursing staff often think of 'patching' as of secondary importance to more immediate and potentially life preserving interventions.

To what extent does inadequate patching—or indeed no patching at all—increase the ocular hazard posed by phototherapy? In fact there is little evidence that phototherapy has caused retinal damage in human infants. This may be due partly to limited follow up testing, and partly to the fact that subtle damage may go undetected. Most studies, however, have reported carefully 'patched' infants who may not be expected to suffer damage.[8]

Animal experiments

The case for routine patching of infants' eyes during phototherapy is mostly based on extrapolations from animal studies. Here an important distinction must be made between the substantial number of reports about ocular phototoxicity[9] [10] and the relatively few studies that have, in an attempt to mimic clinical practice, used an appropriate (that is, neonatal) animal with light exposure obtained from a phototherapy unit. Of the latter more relevant studies, Sisson *et al*[11] exposed newborn piglets (36 hours old) to phototherapy for 72 hours. In contrast to human neonates, the piglets' pupils were dilated to compensate for their orientation at 90° to the light source. At necropsy pronounced histological damage to rod and cone photoreceptors was found, and this was attributed to the light exposure. In a similar study, Messner *et al*[12] found retinal damage in the eyes of newborn monkeys that were exposed to phototherapy for up to seven days; in this experiment, however, the animals were restrained so that they directly faced the light source.

Neither of these studies accurately represents the conditions prevailing in clinical practice. Firstly, human neonates undergoing phototherapy are never purposely restrained to face the light source, nor will their pupils be kept dilated during treatment. Secondly, the amount of time the experimental animals spent with their eyes open was not addressed; studies in humans have shown that premature neonates may spend more than 80% of the time with their eyes fully closed.[13] [14] If the transmission of light through the closed eyelids is similar to that of the adult, there will be a wavelength dependent reduction in the intensity of light reaching the cornea of between 10 to 100 times.[15]

The developing human eye

Consideration of the developing human eye emphasises that further caution is warranted when extrapolating from animal studies. For example, corneal haze[16] and the transient tunica vasculosa lentis (present in the eye of the premature neonate until about 34 weeks' gestation) may reduce the intensity of light reaching the retina. Though photoreceptors in the peripheral retina of the human neonate are relatively well developed at full term, the macular region remains poorly differentiated.[17] [18] Similarly, retinal vascular development is not complete until just after term.[15] The relevance of these observations to ocular phototoxicity in human neonates has yet to be addressed but they highlight the difficulties of extrapolating from animal experiments.

Conclusions

We conclude that further research is required to evaluate the ocular hazard posed by phototherapy.

Firstly, future animal studies should be designed in such a manner as to ensure that the conditions prevalent in clinical practice are appropriately simulated. Secondly, estimates of typical exposures of the retina received by infants during phototherapy are currently unavailable and would be of great benefit in evaluating the potential hazard. To this end we are attempting to measure both the environmental (for example, the intensity and duration of light exposure) and biological (for example, eyelid opening, pupil size, transmittance of the eyelids, and optic media) factors that influence retinal exposure during phototherapy. It is hoped that such data can be related to known photobiological dose response associations obtained from in vivo and in vitro laboratory studies.

Should phototherapy be found to pose an important ocular hazard then the use of eyeshields needs to be afforded the appropriate clinical priority. If it is not, then the economics of 'patching' and its unknown effects on visual development may not justify the continuation of the practice.

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Original articles

Monitoring in non-traumatic coma. Part I: invasive intracranial measurements

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SUMMARY The arterial blood pressure, intracranial pressure, and organ system failure scores were reviewed for 49 infants and children with non-traumatic coma from various causes. The neurological outcome was good in 21 patients, moderate in five, and poor in 23. There was no significant difference in maximum intracranial pressures between patients with a good outcome and those with a poor one, but patients with a poor outcome had significantly lower minimum cerebral perfusion pressures. During the period of admission 18 patients had cardiovascular failure, nine had renal failure, and two developed severe coagulopathy. Seventeen of the 19 patients in whom at least one of these systems failed died.

Our findings emphasise the diversity of illnesses associated with raised intracranial pressure in children and the number who develop multiple organ failure, and the values and limitations of using minimum cerebral perfusion pressure and the organ system failure scores as guides to severity of illness and prognosis.

In children and infants with acute non-traumatic cerebral insults, the intracranial pressure may be monitored invasively to give warning of impending brain tissue shifts[1] and to allow indirect assessment of cerebral perfusion. For clinical purposes the cerebral perfusion pressure was taken to be the difference between the mean arterial blood pressure and the mean intracranial pressure

The value of reducing raised intracranial pressure and of maintaining an adequate cerebral perfusion pressure has been shown in studies of outcome in infections of the central nervous system, and cerebral ischaemia,[2] and Reye's syndrome.[3] In these, the minimum cerebral perfusion pressure was a better guide to prognosis than the peak or maximum intracranial pressure alone; a minimum cerebral perfusion pressure of about 40 mm Hg can be viewed as a watershed with poor neurological outcome below this pressure and likely good outcome above it.[3]

Overall severity and an estimate of probable outcome of the illness may also be assessed by scoring systems such as the clinical classification system[4] and the organ system failure criteria for infants and children.[5]

A review of a heterogeneous group of children with non-traumatic cerebral insults was undertaken to determine the influence of minimum cerebral perfusion pressure and maximum intracranial pressure on outcome, as well as the value of clinical severity scores in documenting progress and indicating outcome.

Patients and methods

In this retrospective study we have reviewed the experience in the paediatric intensive care unit at this hospital during the two years January 1985 to December 1986. Forty nine children presented with acute non-traumatic cerebral insults and had their intracranial pressures monitored as part of their management. There were 29 girls and 20 boys aged 0·06 to 13·06 years (median 3·3). Seventeen children had infections of the central nervous system, 14 had metabolic encephalopathies, seven had suffered ischaemic damage, and 11 had various other conditions (table 1).

The clinical classification grade[4] (table 2) assigned on admission and the observations and investigations made each day were reviewed, and all patients were categorised using the clinical classification system[4] and the organ system failure criteria for infants and children (table 3).[5] Data collected included seizures in the 24 hour period before or after admission and the presence of 'deep coma' (fixed dilated pupils, or a Glasgow coma score[6] of 5

Table 1 *Details of 49 patients studied*

Case no	*Age (years)*	*Sex*	*Diagnosis*	*Cerebral perfusion pressure*	*Intracranial pressure*	*Seizures*	*Deep coma*	*First EEG*	*Worst EEG*	*Outcome*
Infections of the central nervous system (n=17).										
1	0·87	Female	*H influenzae* meningitis	55	10	Yes	No	Ib	—	Poor
2	1·64	Female	*H influenzae* meningitis	55	15	Yes	No	I	I	Good
3	3·11	Male	*H influenzae* meningitis	74	26	No	No	I	I	Good
4	1·57	Male	*H influenzae* meningitis	40	35	No	No	I	II	Moderate
5	0·06	Female	Group B streptococcal meningitis	F	F	Yes	Yes	c	IIc	Died
6	2·15	Female	Meningococcal meningitis	5	65	Yes	Yes	III	III	Died
7	3·82	Male	Tuberculous meningitis	F	F	Yes	No	I	I	Died
8	1·53	Female	Tuberculous meningitis	32	18	No	No	III	III	Died
9	4·95	Female	Measles encephalitis	42	33	Yes	No	Ib	Ib	Good
10	7·27	Male	Epstein-Barr virus encephalitis	62	30	Yes	No	I	I	Good
11	3·08	Male	Viral encephalitis	75	15	Yes	No	I	I	Good
12	10·70	Male	Viral encephalitis	68	30	Yes	No	I	I	Good
13	3·50	Female	Viral encephalitis	55	35	No	No	N	—	Good
14	1·33	Female	Viral encephalitis	41	33	Yes	No	I	I	Good
15	11·10	Male	Viral encephalitis	38	45	Yes	No	I	I	Died
16	13·10	Male	Viral encephalitis	65	20	Yes	No	I	I	Good
17	0·61	Male	Viral encephalitis	73	17	Yes	No	N	I	Good
Metabolic illnesses (n=14)										
18	7·15	Female	Hepatic failure (hepatitis A)	48	33	No	No	I	I	Good
19	12·30	Female	Diabetic ketoacidosis	60	43	No	No	I	I	Good
20	6·67	Male	Propionic acidaemia	42	12	No	No	N	—	Moderate
21	0·49	Female	Methylmalonic acidaemia	42	22	No	No	I	—	Good
22	7·12	Female	Maple syrup urine disease	30	14	No	No	I	III	Died
23	4·37	Female	Maple syrup urine disease	45	50	Yes	No	I	I	Good
24	3·30	Male	Type I GSD hypoglycaemia	50	48	Yes	No	a	I	Good
25	1·07	Female	Postoperative hypoglycaemia	F	F	Yes	Yes	Ib	IIb	Died
26	5·49	Male	Postoperative hypoglycaemia	40	54	No	Yes	I	III	Died
27	5·66	Female	Reye's syndrome like illness	19	67	No	Yes	II	III	Died
28	1·47	Male	Medium chain acyl COA DH deficiency	50	55	Yes	No	Ib	I	Moderate
29	8·60	Female	Reye's syndrome	15	30	Yes	Yes	I	III	Died
30	11·90	Female	Reye's syndrome	64	21	No	No	I	I	Good
31	0·51	Male	Reye's syndrome—chicken pox	31	47	Yes	Yes	c	IIb	Poor
Ischaemic illnesses (n=7)										
32	1·96	Male	Near drowning	44	26	No	Yes	I	I	Poor
33	7·77	Female	Near drowning	54	29	No	Yes	II	IIb	Died
34	8·85	Female	Near drowning	61	23	No	No	N	—	Good
35	2·50	Female	Cardiac arrest—epiglottitis	63	22	No	Yes	III	III	Died
36	1·56	Male	Cardiac arrest—25% burns	20	55	No	Yes	II	III	Died
37	0·35	Male	Sudden infant death syndrome —near miss	38	28	Yes	No	c	I	Moderate
38	0·14	Female	Intraventricular haemorrhage	F	F	Yes	No	Nb	—	Moderate
Other illnesses (n=11)										
39	3·23	Female	Polyarteritis nodosum	40	76	Yes	No	I	III	Died
40	0·65	Female	Encephalopathy of unknown aetiology	59	20	Yes	No	IIc	IIc	Poor
41	0·83	Female	Staphylococcal empyema	46	26	No	No	N	—	Good
42	3·72	Female	Hypothalamic astrocytoma	57	30	No	No	ND	ND	Good
43	5·53	Female	Ventriculoperitoneal shunt blockage	55	22	Yes	No	Ib	—	Good
44	11·80	Male	Acute hydrocephalus	57	43	No	No	N	I	Good
45	10·20	Male	Hypertensive encephalopathy	F	F	Yes	No	III	III	Died
46	1·70	Female	Subarachnoid haemorrhage	30	50	Yes	No	II	II	Poor
47	1·45	Male	Encephalopathy—neuroblastoma	62	45	Yes	No	Ib	III	Poor
48	8·45	Female	Haemolytic uraemic syndrome	25	41	Yes	No	c	IIc	Died
49	3·52	Female	?Haemolytic uraemic syndrome	45	10	Yes	Yes	I	III	Died

ND=not done, F=failed monitoring

or less not attributable to drugs) on admission. Electroencephalograms were graded according to the criteria given in table 4. The time between the first sign of depressed consciousness and the initiation of intracranial monitoring was also noted for each patient.

The intracranial pressure was monitored using a subarachnoid screw (Codman ICP system) in 33 patients, a fluid filled intraventricular catheter in 13, and a subdural transducer (Gaeltec pressure transducer model ICT/b) in three. The subarachnoid screw was generally used in the older children, the limitation being the thickness of the skull vault. The youngest child monitored with this technique was 6 months old. The ventricular and subdural systems were used at all ages. Morbidity was low, with no haemorrhages, and only one case of infection (with the ventricular catheter). The median duration of monitoring was three days (range 0·5 to 16). Arterial blood pressure using a transduced intra-arterial cannula was shown on the same bedside monitor as the intracranial pressure (Hewlett Packard patient monitor 78353A or 78354A). Intracranial pressure and blood pressure measurements were charted half hourly, and during unstable periods such as acute rises in intracranial pressure or falls in blood pressure, or both. The highest intracranial pressure and lowest cerebral perfusion pressure measurements in the first 12 hours of monitoring, as well as the maximum intracranial pressure and minimum cerebral perfusion pressure for the period of monitoring, were recorded for each patient either from the half hourly measurements or from the measurements during the acute episodes if they lasted more than two minutes.

Table 2 *Clinical classification system*[4]

Class I	Patient not requiring intensive care
Class II	Patient requiring overnight observation
Class III	Physiologically stable patient requiring intensive nursing and monitoring
Class IV	Physiologically unstable patient requiring intensive care from nurses and doctors and frequent reassessment and adjustment of treatment

Table 3 *Criteria for organ system failure for infants and children*[5] *Failure for a system defined by meeting at least one of the criteria*

System and measurement	*Criteria*
Cardiovascular:	
Systolic blood pressure	<40 mm Hg* <50 mm Hg†
Heart rate	<50 or >220/minute* <40 or >200/minute†
Serum pH	<7·2 with normal $PaCO_2$
Cardiac arrest	
Continuous infusion of inotropic agent to maintain blood pressure or cardiac output, or both	
Respiratory	
Respiratory rate	>90/minute* >70/minute†
$PaCO_2$	>8·6 kPa
PaO_2	<5·3 kPa in the absence of cyanotic heart disease
PaO_2 (mm Hg) divided by the oxygen tension in inspired air	<200 in the absence of cyanotic heart disease
Mechanical ventilation for longer than 24 hours postoperatively	
Neurological:	
Glasgow coma score[5]	<5
Fixed dilated pupils	
Haematological:	
Haemoglobin concentration	<50 g/l
White cell count	<3·0×10⁹/l
Platelet count	<20×10⁹/l
Renal	
Serum urea concentration	>13 mmol/l
Serum creatinine concentration	≥180 µmol/l in the absence of pre-existing disease
Dialysis	

*=less than 1 year old, †=1 year old or more.

Table 4 *Criteria for grading of electroencephalograms*

Predominant activity	
N	— Normal or borderline for age and state
I	— Slow activity (0·5–3 cycles/second) or periods of low amplitude (<50 µV), or both, of less than five seconds duration
II	— Generalised low voltage activity (<50 µV)
III	— Electrocerebral silence (isoelectric)
Discharges	
a	— Continuous and unchanging (status epilepticus)
b	— Isolated (focal or multifocal)
c	— 'Electrical storms' (runs of discharges changing in amplitude, rate, and morphology with shifting focal distribution)

These patients were managed similarly using standard nursing and therapeutic measures[7 8] Specific nursing care included attention to body position with head tilt up at 25–30°, the avoidance of neck compression, and the maintenance of normal core temperature. Factors known to precipitate episodes of raised intracranial pressure such as endotracheal suction, physiotherapy, movement, and chest radiographs were anticipated and treated, first with hyperventilation, then with thiopentone. The aim of treatment was to reduce the intracranial pressure to 15 mm Hg or less and to maintain the cerebral perfusion pressure above 50 mm Hg. The protocol included mechanical hyperventilation (the $PaCO_2$ being lowered to 3·3–4·0 kPa), paralysis, and sedation with pancuronium, diazepam, and morphine (each 0·1 mg/kg/dose), phenobarbitone (standard dose for age and weight), osmotherapy (to 300–310 mmol/l) with intravenous mannitol and frusemide, and drainage of cerebrospinal fluid through a ventricular catheter. Patients with labile raised intracranial pressure who did not respond to these measures were given thiopentone, either intermittently or by infusion. Restoration of a satisfactory cerebral perfusion pressure was achieved by increasing the mean systemic arterial blood pressure with infusions of colloid or continuous infusions of dopamine, or both. Fifteen patients required thiopentone, and six required dopamine.

Outcome of the survivors was assessed from outpatient reviews at this hospital or from questionnaires completed at referring units The median time of assessment of the survivors was 8·0 months (range 1–24) after the initial illness. Neurological outcome was graded using a simplification of the outcome scale proposed by Seshia *et al* (table 5).[9]

Statistical analyses were by Student's *t* test, the Mann-Whitney U test, and Levin and Bertell's estimate of population attributable risk applicable to retrospective studies.[10]

Results

Twenty six of the 49 patients had a good or moderate neurological outcome, and 17 died during the acute illness. The remaining six children had severe neurological deficits.

Table 5 *Neurological outcome in survivors The worse group is selected if there is a dissociation between the neurological and developmental states*

Group	*Neurological state*	*Development (handicap)*
Good	Normal, seizures if present well (100%) controlled	None
	or	
	Minimal alteration of tone or deep reflexes, isolated cranial nerve palsy, mild weakness (grade 4) or ataxia, seizures if present fairly well controlled (99–75%)	Mild
Moderate.	Moderate weakness (grade 3) or ataxia, behaviour disturbance, cranial nerves severely affected, seizures moderately controlled (74–50%)	Moderate
Poor	Severe weakness (<grade 3) or ataxia, tetraplegia, uncontrolled seizures (<50%)	Severe

INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE MEASUREMENTS

All patients had received some treatment to reduce intracranial pressure before monitoring and the institution of full neurointensive care. When the patients who had good outcomes were compared with those who had poor outcomes, the interval between the first sign of depressed consciousness and the initiation of monitoring was significantly shorter in those who had a good outcome, with the respective range (median) being 0·0–1·0 (0·5) days and 0·5–5·0 (1·0) days, respectively, $p<0·05$ Complete data about monitoring were available in 44 patients, 40 of whom had intracranial pressures of 15 mm Hg or more at some time during monitoring.

In the first 12 hours of monitoring there was no difference between the highest intracranial pressure and lowest cerebral perfusion pressure in those with good, and those with poor outcomes The means (SD) in the two groups were 22·1 (8·0) mm Hg and 27·6 (15·7) mm Hg (intracranial pressure) and 65·1 (11·8) mm Hg and 56·3 (22·2) mm Hg (cerebral perfusion pressure). For the duration of monitoring,

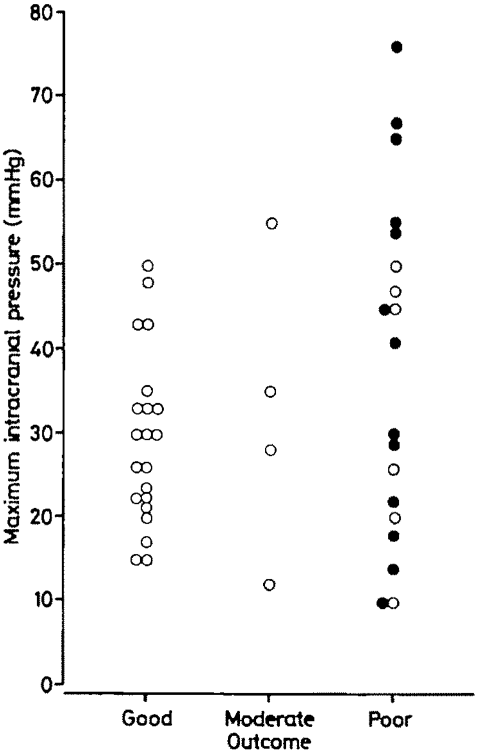

Fig 1 *Maximum intracranial pressure for the period of monitoring, and outcome in 44 patients with complete data; ●=patients who died during the acute illness*

however, though the maximum intracranial pressure was similar in the two groups—29·3 (10 3) mm Hg and 38·1 (20·1) mm Hg (fig 1)—lower minimum cerebral perfusion pressures were found in those who had poor outcomes, 56 9 (10·6) mm Hg and 37·2 (16·6) mm Hg, respectively, p<0·001 (fig 2).

All patients who had good outcomes had minimum cerebral perfusion pressures that did not go below 40 mm Hg. Fourteen patients had perfusion pressures of 40 mm Hg or less, 12 of whom had a poor, and two a moderate outcome. There were nine children with minimum cerebral perfusion pressures in the range 38–42 mm Hg whose outcomes were distributed equally among the three groups (fig 2).

In seven patients who had poor outcomes, cerebral perfusion pressure during the period of monitoring was always greater than 42 mm Hg and we therefore reviewed the clinical features of these patients more fully. In two (cases 1 and 49) the maximum intracranial pressure during monitoring was below 15 mm Hg. Case 1 had had an episode of status epilepticus lasting at least one hour two days before monitoring. The clinical course of case 49 before monitoring was complicated by disseminated intravascular coagulation, hypoglycaemia, renal failure, and cardiac arrest. The remaining five patients with poor outcomes despite good cerebral perfusion pressures had maximum intracranial pressures above 15 mm Hg (range 20–45). Three of these (cases 32, 33, and 35) had been resuscitated after cardiorespiratory arrest before monitoring Of the other two children, one (case 40) had had two diagnostic lumbar punctures with neurological deterioration after each, the second being performed 24 hours before admission. The other (case 47) had a maximum intracranial pressure of 45 mm Hg and a minimum cerebral perfusion pressure of 62 mm Hg This apparently adequate cerebral perfusion pressure therefore reflected systemic hypertension rather than the intracranial state.

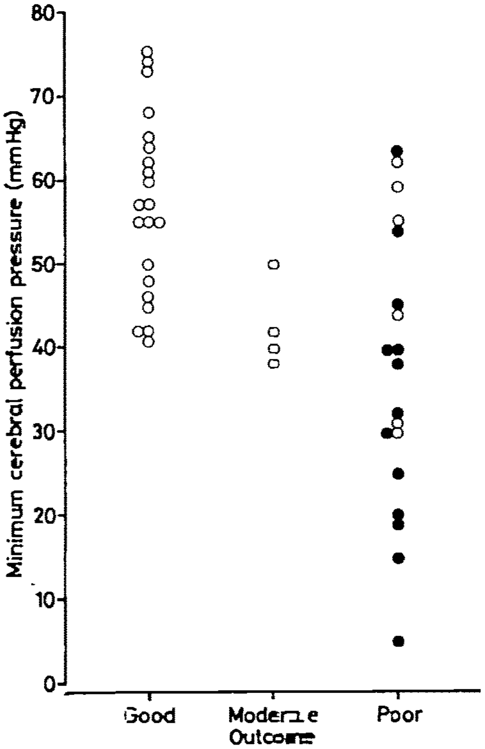

Fig 2 *Minimum cerebral perfusion pressure for the period of monitoring, and outcome in the patients with complete data. ●=patients who died during the acute illness*

In summary, 12 of the 14 patients with minimum cerebral perfusion pressures of 40 mm Hg or less had poor outcomes compared with seven out of 30 patients with minimum cerebral perfusion pressures greater than 40 mm Hg. Review of the age, sex ratio interval between the first sign of depressed consciousness and initiation of monitoring, diagnostic categories, and proportion with seizures either before or after admission, were similar when the patients with minimum cerebral perfusion pressures of 40 mm Hg or less were compared with those with minimum cerebral perfusion pressures greater than 40 mm Hg (table 6). Using Levin and Bertell's estimate of population attributable risk applicable to a retrospective study,[10] the estimated risk of poor outcome attributable to a minimum cerebral perfusion pressure of 40 mm Hg or less is R_A=0 6 (95% confidence interval 0·26 to 0·78), so assuming low cerebral perfusion pressure to be a major determinant of poor outcome, if minimum cerebral perfusion pressures of 40 mm Hg or less could be avoided, poor outcome could be reduced by between 26 and 78%.

SCORING SYSTEMS

On admission 44 patients (90%) were in the most severe category of the clinical classification system. The remaining five patients were in class III The mortality during the acute illness of patients who were in class IV on admission was 36% (16 of 44).

Sedation, paralysis, and ventilation meant that the criteria for failure in the neurological system in the organ systems failure scoring system could not be assessed adequately and consistently in all patients for each day of admission. Those in deep coma however, could be identified. On admission there were 12 such patients and all had poor outcomes Measurement of intracranial pressure

Table 6 *Comparison of patients whose minimum cerebral perfusion pressures were >40 with those ≤40 mm Hg*

Details of patients	*Minimum cerebral perfusion pressure*	
	>40 mm Hg (n=30)	*≤40 mm Hg (n=14)*
Sex ratio (male female)	13 17	6·8
Age (years)		
Range	0-49–13 06	0·35–11 1
Median	3 5	2 69
Diagnostic group		
Infection of the central nervous system	11	4
Metabolic illness	8	5
Ischaemic illness	4	2
Other illness	7	3
Time from first sign of depressed level of consciousness to initiation of monitoring (days)		
Range	0–5·0	0·5–4
Median	1 0	1·0
Patients with seizures	16	8
Outcome		
Good	21	—
Moderate	2	2
Poor	7	12

was unsuccessful in two of the 12, and in the other 10 the range and median of the cerebral perfusion pressure were 5–63 and 36 mm Hg, respectively

All patients were ventilated during the course of their illnesses. A score for the respiratory system did not differentiate between those with true respiratory failure and those who were ventilated solely for treatment. The organ system failure scoring was therefore limited to the cardiovascular, renal, and haematological systems

At the end of the first day of admission nine of the 49 patients had failure of at least one of these systems. During the period of admission the cardiovascular system failed in 18 patients, the renal system in nine, and the haematological system in two Nineteen patients (39%) had at least one of the systems fail at some time during their admission, and of these 17 had poor outcomes.

Discussion

The diversity of illnesses associated with raised intracranial pressure has been recognised before,[1] and this review not only confirms this but also emphasises that many of these children have multiple organ failure. This finding is important, and contributes to the high mortality and morbidity.

The maximum intracranial pressure is an unreliable guide to prognosis as the difference between the groups with good and poor outcomes was not clinically relevant. Indeed, intracranial pressures greater than 40 mm Hg were found in three patients whose eventual outcomes were good. All children with intracranial pressures above 55 mm Hg, however, had poor outcomes (fig 1).

These data confirm previous reports[3] that the cerebral perfusion pressure is a better guide than the intracranial pressure to eventual neurological outcome, and values around 40 mm Hg seem to be critical. It must be noted, however, that in this series the values in the first 12 hours of monitoring were not significantly different between those with good and those with poor outcomes.

Despite the observation that none of the patients with a cerebral perfusion pressure below 40 mm Hg had a good outcome, there were patients with apparently adequate cerebral perfusion pressure who had poor outcomes. In those in whom there had been a delay between the initial cerebral damage and monitoring, and those in whom the damage was due to hypoxia or complex pathophysiology, the eventual outcome may have reflected the severity of the cerebral damage that occurred before monitoring.[11] In addition, patients with raised intracranial pressure and acute systemic hypertension had cerebral perfusion pressures that reflected the degree of hypertension rather than the intracranial state. It must also be emphasised that there were nine patients who had minimum cerebral perfusion pressures in the range 38–42 mm Hg. Neurological outcome in these patients was distributed equally in the good, moderate, and poor groups. This suggests that prognosis based on cerebral perfusion pressure alone is unreliable when values are in this borderline range.

This study has taken no account of time spent at different cerebral perfusion pressures or of the responsiveness of intracranial pressure to treatment. It may be that the differences in outcome could be further explained by these factors. Despite their limitations these retrospective data strongly suggest that neurological outcome in comatose children may be improved if cerebral perfusion pressure can be maintained above 40 mm Hg. This could be achieved by earlier recognition of children at risk of raised intracranial pressure, and rapid initiation of adequate monitoring in order to prevent episodes of poor cerebral perfusion.

Intracranial measurements can give an indication of intracranial fluid and tissue dynamics for the period of monitoring. They give no indication, however, of the severity of the cerebral insult and of cerebral function before and during monitoring. Non-invasive measurement of cerebral function in the paralysed and ventilated state may provide an improved guide to prognosis, and the role of electroencephalography in these patients has been reviewed.[11]

The clinical classification system[4] was helpful in classifying patients broadly with respect to need on admission to the intensive care unit Most, however, were in class IV and those most severely affected were not specifically identified. The organ system failure criteria for infants and children[5] was not entirely successful. It was limited because of the difficulty of neurological assessment for the purpose of comparative scoring in patients with changing degrees of paralysis and sedation, and differing degrees of cerebral damage. All the patients identified with either fixed dilated pupils or a Glasgow coma score less than 5 not attributable to drugs, however, had a poor outcome. The role of clinical neurophysiology in this context has also been discussed.[11] Furthermore, the finding of respiratory failure did not differentiate primary lung problems, true central respiratory depression and paralysis, or sedation and ventilation as part of treatment. Despite these limitations, failure in at least one of the systemic systems (cardiovascular, renal, or haematological) led to a more precise identification of those likely to have poor outcome. This was also a simple means of documenting deterioration or the need for increased support during the acute illness

Though the early recognition of raised intracranial pressure is fraught with problems we conclude that all patients with non-traumatic cerebral insult complicated by raised intracranial pressure or at risk of developing it, should be considered for measurement of intracranial pressure and invasive arterial monitoring at an early stage of their illnesses in order to prevent periods of inadequate cerebral perfusion pressure. In addition, the use of a limited organ system failure assessment provides valuable information both as a guide to prognosis and as a more objective assessment of severity.

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Monitoring in non-traumatic coma. Part II: electroencephalography

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SUMMARY Forty eight comatose children had electroencephalograms (EEG) recorded during the acute phase of their illnesses. These were classified according to a simple grading system and the findings correlated with the presence of seizures, deep coma, minimum cerebral perfusion pressure, and eventual neurological outcome. Serial EEGs proved important, particularly when slow activity was seen initially. None of the 20 patients who showed low amplitude EEG activity or electrocerebral silence at any stage of the acute illness did well. Discharges were seen in only 13 of the 29 patients with seizures and their presence did not correlate with outcome except in five patients with a distinctive pattern of discharges, none of whom had a good outcome. EEG findings associated with poor outcome did not always correlate with the clinical assessment of deep coma, emphasising the difficulties of neurological evaluation in these patients. Five of the patients with cerebral perfusion pressures greater than 42 mm Hg had a poor outcome that was predicted by serial EEGs. In nine patients with a minimum cerebral perfusion pressure in the borderline range 38–42 mm Hg the EEG was useful as an indication of the outcome.

The EEG reflects changes in cerebral function which may be due to multifactorial or repeated insults. An EEG is therefore important in both the initial assessment and as an indicator of the neurological outcome, particularly in those patients in whom the cerebral perfusion pressure has apparently been adequate or within the borderline range.

Clinical findings in comatose patients whose intracranial pressure is being monitored are influenced by the underlying neurological condition and by drug treatment. The minimum cerebral perfusion pressure measured during the acute illness, although useful, is only a limited guide to prognosis because it gives no indication of the severity of the preceding cerebral damage or of changes of cerebral function during monitoring.[1]

In children with acute non-traumatic cerebral damage, the electroencephalogram (EEG) provides information about the severity and distribution of altered function of the cerebral cortex, presence of discharges, and even (on occasion), a clue to the possible aetiology. In Reye's syndrome,[2] near drowning,[3] and after cardiac arrest[4] the EEG taken at an early stage was of practical help in assessing the final neurological outcome. As only nine of the 49 children already reviewed[1] presented with one of these three conditions, we have asessed the contribution of the EEG findings to the assessment of prognosis in this larger more heterogeneous group of comatose children. Particular attention was paid to the association between intracranial measurements and EEG features.

Patients and methods

Forty eight of the 49 children previously reported[1] had EEGs recorded in the paediatric intensive care unit during the acute phase of their illness. All EEGs were recorded at the bedside using Grass 8 channel EEG machines and previously described techniques [4] The EEGs were usually recorded within 24 hours of admission, and no longer than 36 hours in any patient One hundred and sixty two EEGs were carried out on the 48 patients during 351 patient days in hospital. Eight children had only one EEG, but serial EEGs were taken in most (two in 13, three in 9, and four or more in 18 children)

The EEGs were graded in order of severity into one of the four categories defined in part I.[1] This grading was adapted from systems used previously in patients with Reye's syndrome,[2] near drowning,[3] and after cardiac arrest,[4] and like these was based mainly on the amplitude of the predominant activity.

In addition to this, however, those EEGs showing discharges were given one of three subscripts indicating the type of discharges. In nine patients receiving thiopentone the EEG grades of II (low amplitude <50 μV) or III (isoelectric) were not included in the data analysis. In these cases the EEG grades before the drug was given and after the drug had cleared were used. Attempts to stimulate the patients were made during each recording but environmental conditions made this difficult to assess and so it has not been included in this study. Although the recordings were reviewed retrospectively there was little discrepancy between the original report and the subsequent grading.

Clinical findings including seizures in the 24 hour period before or after admission, and deep coma (fixed dilated pupils, or a Glasgow coma score of five or less not attributable to drugs) on admission, were noted. Maximum intracranial pressure and minimum cerebral perfusion pressure together with the neurological outcome[1] were correlated with EEG grading scores.

The χ^2 test with Yates's correction was used to assess the differences between proportions.

Results

The diagnosis, neurological outcome, and EEG findings were listed previously.[1] The association between the initial EEG and the eventual outcome is shown in table 1. In five patients (cases 5, 24, 31, 37, 48[1]) the initial EEG could not be graded for background activity because of the presence of continuous discharges

All nine patients whose initial EEG showed low amplitude activity (grade II) or electrocerebral silence (grade III) had a poor neurological outcome. Nineteen of the 34 patients in whom the initial EEG was either normal or showed slow activity (grade I) did well; the remainder had either moderate (n=4), or poor (n=11) outcomes.

In the 40 children who had serial EEGs the worst EEG grade was correlated with outcome (table 2). None of the 20 patients with either grade II or grade III at any stage did well. Indeed, 19 of these 20 patients had poor outcomes. Fifteen of the 20 patients with grade I as their worst grading did well, but two had moderate, and three had poor outcomes. The association between grade II or III EEG and poor outcome was highly significant (p<0·001)

Table 1 *Initial EEG grade in relation to eventual neurological outcome (n=43)*

Initial grade	*Outcome*		
	Good	*Moderate*	*Poor*
Normal	5	2	0
I	14	2	11
II	0	0	5
III	0	0	4

Table 2 *Worst EEG grade in the 40 patients with serial studies in relation to eventual outcome*

Worst grade	*Outcome*		
	Good	*Moderate*	*Poor*
Normal	0	0	0
I	15	2	3
II	0	1	7
III	0	0	12

The five children (cases 7, 15, 28, 32, 37) who had either moderate or poor outcomes despite grade I EEGs had additional EEG features that were not present in those who did well In three children (cases 15, 28, 32) there was no clinical or EEG improvement 9–12 days after the initial insult (fig 1). This is in pronounced contrast to the patients who did well, in whom the grade I pattern only was seen for a maximum of six days before a clinical improvement in the level of consciousness was noted. Cases 7 and 37 had focal low amplitude activity, and case 37 also had seizures that were difficult to control, with 'electrical storms' being recorded at presentation and 36 hours later. Although brief episodes of low amplitude activity occurring either spontaneously or in response to stimuli were a prominent feature in the EEGs of case 15, similar features were present though less pronounced in some patients who did well.

Twenty nine patients had clinical seizures in the 24 hours before or after admission; only 13 of these had discharges in the initial record and their outcomes are compared with those of patients without discharges in table 3. There was no difference in outcome between patients with or without discharges except that none of the five patients with 'electrical storms' in the initial EEG recording (fig 2) did well, and the clinical seizures in these five patients were difficult to control.

Of the 12 patients presenting in deep coma, two initially showed electrocerebral silence (grade III). Low amplitude background activity (grade II) was seen in a further three patients. Slow activity (grade I) was present in five patients, and two could not be graded because of continuous 'electrical storms'. Review of the worst EEGs in these children showed that seven had grade III, and four others had grade II tracings. The EEG in the twelfth

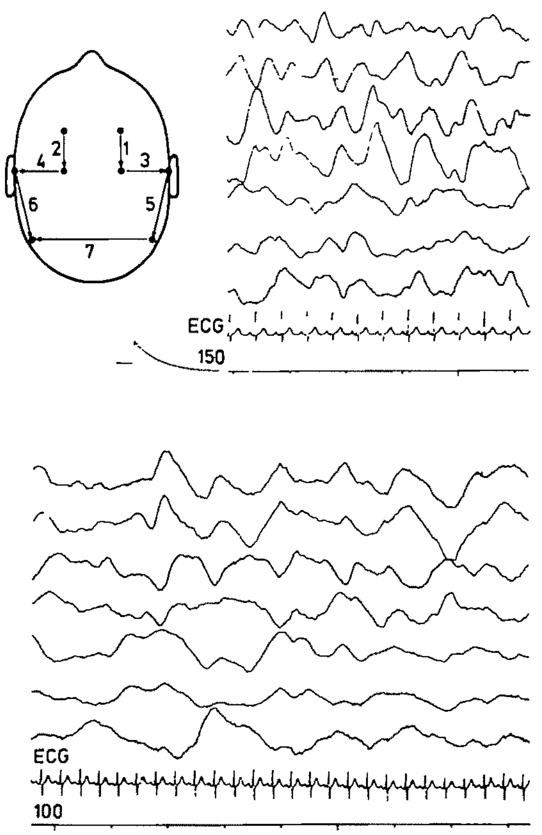

Fig 1 *An infant aged 18 months with a metabolic encephalopathy (case 28) had generalised large amplitude slow activities (grade I) on initial EEG (upper trace) Nine days later (lower trace) slow activity is even more prominent though still grade I. He had adequate cerebral perfusion pressure throughout and survived with a moderate handicap*

Table 3 *Relation between discharges in the initial EEG and eventual outcome*

Discharges	*Outcome*		
	Good	*Moderate*	*Poor*
None	17	2	16
Continuous (a)	1	0	0
Isolated (b)	2	2	3
'Electrical storms' (c)	0	1	4

patient (case 32), although grade I, never improved. In addition two patients (cases 8 and 45) with grade III, and two (cases 40 and 46) with grade II, initial EEGs were not deeply comatose. In the two cases with grade III tracings, muscle relaxants and cycloplegics had been given shortly before admission.

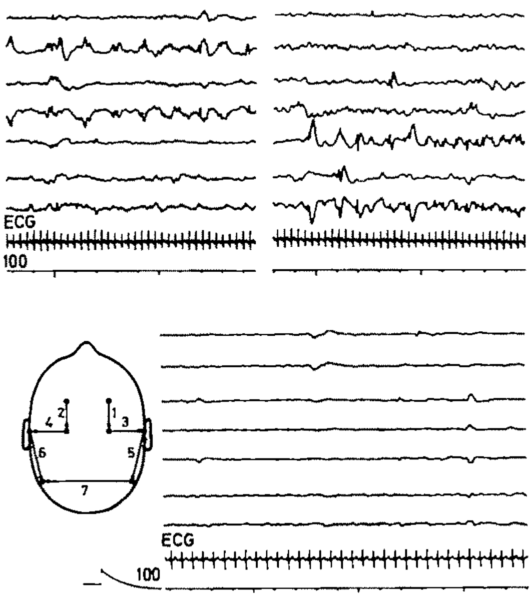

Fig 2 *An infant aged 6 months with Reye's syndrome after chickenpox (case 31) showed an unusual EEG picture; runs of discharges shifting in distribution and changing in both rate and morphology ('electrical storms') were seen in the initial EEG (upper traces) He had seizures that were difficult to control. EEG tracings gradually deteriorated and 14 days later were of low amplitude (grade II) (lower trace) He survived with severe neurological impairment.*

The worst EEG was grade II or III in all nine patients with minimum cerebral perfusion pressure less than 38 mm Hg, and they all had poor outcomes.[1]

There were 20 patients with serial EEGs who had minimum cerebral perfusion pressure greater than 42 mm Hg, and their outcome is shown in table 4. Although most remained no worse than grade I (with a good outcome), there were seven patients (cases 1, 32, 33, 35, 40, 47, and 49) with poor neurological outcomes.[1] Five of these had EEGs of grade II or III, and of the other two children case 32 (although grade I throughout) never improved, and case 1 did not have serial investigations.

Table 4 *Worst EEG grade (serial studies) in 20 patients with adequate cerebral perfusion pressure (>42 mm Hg)*

Worst grade	*Outcome*		
	Good	*Moderate*	*Poor*
I	13	1	1
II	0	0	2
III	0	0	3

Table 5 *Worst EEG grade (serial studies) in relation to outcome in seven patients with cerebral perfusion pressures of 38–42 mm Hg*

Worst grade	*Outcome*		
	Good	*Moderate*	*Poor*
I	2	1	1
II	0	1	0
III	0	0	2

In the nine children whose minimum cerebral perfusion pressure was in the borderline range (38–42 mm Hg) the outcomes were equally distributed among the three groups, three were good, three moderate, and three poor. The worst EEG in relation to outcome in the seven of them who had serial studies is shown in table 5. Two of the three patients (cases 26 and 39) with poor outcomes had grade III tracings (electrocerebral silence). The third patient (case 15) had brief episodes of low amplitude activity (but was classified as grade I). Two of the three patients (cases 9 and 14) with good outcomes had serial EEGs and they remained grade I. Two of the three patients with moderate outcomes had serial EEGs and the worst grade was II in case 4, and I in case 37. In addition, in the latter case 'electrical storms' had initially been recorded.

Of the five patients in whom intracranial pressure monitoring failed, three of the four with poor outcomes showed grade II or III tracings. The fourth patient (case 7) had focal low amplitude activity

Discussion

There are obvious advantages in grading EEG features that may help predict the neurological outcome of a comatose child. The grading used in this series (based mainly on amplitude) was found useful by other authors in specific types of encephalopathy.[2-4] Our results suggest that the grading is valuable in a wider context. All nine patients whose initial EEG showed grade II (low amplitude) or grade III (electrocerebral silence) tracings had poor outcomes, as did 19 of the 20 children who had grade II or III tracings at any stage during their illnesses (excluding EEGs taken when intravenous thiopentone had been given). Only one child (case 4) with a grade II tracing had a moderate neurological outcome. There was never any improvement in the EEGs of patients initially showing either grade II or III tracings.

Moderate to large amplitude (0·5–3 cycles/second) slow activity (grade I) is the usual EEG change associated with any acute encephalopathy or encephalitis and represents a potentially reversible alteration of cerebral function, and it is important to establish this in the early phase of neurointensive care. During the acute phase of the illness, however, further damage is likely to occur, so serial EEG studies are important when grade I is seen initially; eight of our 23 patients later deteriorated to grade II or III. Only 15 of the 20 patients who never had an EEG worse than grade I had a good outcome. Serial studies in the other five showed unusually persistent slow activities without any increase in frequency in three cases, contrasting with the gradual increase in frequency of EEG activities usually seen during recovery. Although less than five second periods of extremely low amplitude (either spontaneously or in response to stimuli) occurred in one patient classified as grade I who had a poor outcome, this EEG feature alone does not seem to have any discriminatory value, as it was noted in some children who recovered fully.

Of the five patients whose initial EEG could not be graded into one of the four categories because discharges were their main feature, one showed clinical and EEG evidence of status epilepticus that was reversible. The 'electrical storms' seen in the other four patients are a distinctive EEG pattern that is commonly associated with damage to the cortical microcirculation and may account for the outcome in these patients. Any neurological sequelae seem to be related to the severity and extent of this underlying process, and four of our five patients who showed 'electrical storms' (one of whom was also initially graded as II) were eventually classified as grade II. Neither the presence of seizures nor of isolated discharges were in themselves pointers to eventual outcome, though repetitive stereotyped discharges (not seen in any of these patients) are highly suggestive of herpes simplex encephalitis. Localised EEG abnormalities, whether discharges or areas of low amplitude, were usually associated with focal neurological signs.

All the patients diagnosed on admission as deeply comatose had poor outcomes[1] and most of these had grade II or III EEG tracings at some time. It was, however, surprising that the EEG was grade I initially in five patients. In addition, two patients with grade III EEG tracings on presentation were not clinically identified as being deeply comatose. Neurological assessment is, however, difficult in sedated and paralysed patients and the EEG may be the best method of assessing cerebral function, though the effects of drugs (such as barbiturates) should be taken into acccount.

The finding that seven patients with no evidence of reduced cerebral perfusion pressure during intracranial pressure monitoring had grade II or III EEGs emphasises that poor cerebral perfusion pressure or raised intracranial pressure are not the only factors producing cerebral damage (though periods of raised pressure with poor cerebral perfusion before monitoring cannot be excluded in all cases). Indeed, when the first EEG shows electrocerebral silence, invasive monitoring of intracranial pressure is contraindicated.

This study shows that serial EEGs are important as a guide to outcome in patients without evidence of poor cerebral perfusion pressure, and are of value in cases with unreliable monitoring In nine patients with borderline cerebral perfusion pressure measurements the EEG seemed to be of value in assessing whether there had been irreversible impairment of cerebral function. Monitoring with a continuous single channel signal processed EEG (Cerebral Function Analysing Monitor)[5] may have a place in the identification of compromised cerebral function caused by episodes of raised intracranial pressure. This is currently being studied in this unit, though in the comatose patient single channel monitoring can never replace serial multichannel EEGs.

The EEG reflects the overall picture of multiple factors that may alter cerebral function including damage from failure of other organs, and the cumulative effects of periods of poor cerebral perfusion pressure.[6] It is not surprising therefore that the EEG has a valuable role in the prognosis of children with the likelihood of raised intracranial pressure complicating non-traumatic coma. Although some recent studies suggested that evoked potentials are more useful and reliable than EEGs as prognostic indicators in comatose patients,[7] [8] evoked potentials only give information about specific pathways and cortical areas and may therefore be misleading when used in isolation. Studies using evoked potentials may, however, be helpful in supplementing the EEG findings—for example, somatosensory evoked potentials are particularly useful in patients receiving barbiturates, and brain stem auditory evoked potentials give information about brain stem function unobtainable from the EEG.[9] The value of studies using both EEG and evoked potentials in a larger group of infants and children with non-traumatic coma will be the subject of a further report.

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Air or oxygen as driving gas for nebulised salbutamol

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SUMMARY The effects of nebulised salbutamol driven by compressed air or oxygen were compared in a randomised crossover study during 27 attacks of acute asthma. Arterial oxygen saturation fell by 2–6% during or after treatment in 10 cases: seven with compressed air, two with oxygen, and one with both driving gases. Hypoxaemia occurred in younger children and in those who fell asleep, but was not related to the level of arterial oxygen saturation before treatment or the size of the response to bronchodilator therapy. More children fell asleep with compressed air nebulisation. Arterial oxygen saturation improved and heart rates remained stable during treatment when oxygen was the driving gas. After treatment, however, arterial oxygen saturation fell and heart rates rose to values that were similar to those after treatment with compressed air. The falls in arterial oxygen saturation we observed, though comparatively small, would be clinically important on the steep part of the oxygen dissociation curve, and our results emphasise that families with home nebulisers should seek medical advice early when their children develop severe asthma. The benefits of using oxygen as the driving gas during nebulisation were transient, and in severe asthma treatment with oxygen needs to be continued after the nebulised salbutamol has been given.

There has recently been a pronounced increase in the use of nebulisers driven by air compressors to treat asthma at home.[1] Nebulisers are an effective way of giving bronchodilators and prophylactic drugs to asthmatic patients who find inhalers difficult to use, and they are particularly useful in the treatment of young children. There are, however, some reasons for concern about the domiciliary use of nebulisers. Firstly, many patients with a home nebuliser have not received adequate instruction for its use.[2] Secondly, some severely asthmatic patients have repeatedly used high doses of bronchodilator by nebuliser instead of seeking medical help, with fatal outcomes.[3] Thirdly, home nebulisers are usually used without supplementary oxygen. Some degree of hypoxia is inevitable during an acute severe asthmatic attack and previous studies have indicated that giving high dose β adrenergic bronchodilators by nebuliser may lead to a further decrease in oxygenation.[4-6]

We therefore investigated the changes in oxygenation during and after nebulised salbutamol given with air or 100% oxygen as the driving gas in children with acute severe asthma. Oxygenation was assessed by the measurement of oxygen saturation with a pulse oximeter, a non-invasive technique that has been shown to reflect hypoxaemia accurately in infants with chronic lung disease[7] and in children over 5 months of age requiring intensive care.[8]

Patients and methods

Any child more than 2 years old who was in hospital with an acute attack of asthma was considered for the study. Our criteria for hospital admission were a peak expiratory flow rate of less than 25% of the predicted value, or failure to respond to an adequate dose of nebulised salbutamol. Eighteen boys and eight girls aged 2 to 12 (median 7) years were studied; one girl was studied on two separate occasions three months apart, making a total of 27 studies. In addition to nebulised salbutamol, 12 were receiving intravenous aminophylline or oral theophylline, and eight were also receiving systemic corticosteroids. The duration of the attack at the time of entry was from 6 to 72 hours (median 29). Up to 18 doses of nebulised salbutamol had been given before entry but the median was two, indicating that most were studied soon after admission to hospital.

The children were given nebulised salbutamol driven by compressed air (Porta-neb 50) and 100% oxygen (8 l/minute) in random order two to four hours apart. We established that the flow rate from the Porta-neb 50 was about 8 l/minute. The children were all awake and breathing room air before each study. The dose was 0·15 mg/kg (to a maximum of 5 mg) diluted to 4 ml with saline. An Inspiron minineb nebuliser pot and medium concentration oxygen mask (inspired oxygen concentration of 50–60% when driven by 100% oxygen at 8 l/minute) were used on each occasion. Other treatment was not altered during the study period. Measurements after completing the nebulised treatment were made with the children breathing room air

Heart, respiratory, and peak expiratory flow rates were recorded before, and 10 to 15 minutes after each treatment. Heart rate was also recorded during treatment. Arterial oxygen saturation was measured continuously using a Biox 3700 pulse oximeter for five minutes before, during, and 15 minutes after each treatment. After preparation of the skin, the finger probe was applied and a continuous digital reading of arterial oxygen saturation was displayed and recorded. The recordings were noted at 30 second intervals and mean values for the five minutes before, the last five minutes during nebulised treatment, and 5–10 and 10–15 minutes after treatment were calculated.

Five children who were receiving nebulised salbutamol four hourly at the time of entry were also studied before, during, and after nebulised saline (4 ml). They were given one of four treatments, two active and two placebo, in random order at two hourly intervals with the proviso that active treatment followed placebo so that we did not interfere with the management if the acute attack. The treatments were: nebulised saline and compressed air; nebulised salbutamol and compressed air, nebulised saline and 100% oxygen, and nebulised salbutamol and 100% oxygen.

The mean arterial oxygen saturation of these children before receiving saline (91·6%) was similar to that recorded before receiving salbutamol (91·9%) in all 27 cases. The maximum individual fall at any time interval with nebulised saline was 1·6%. The coefficient of variation of arterial oxygen saturation (based on 11 values in each case) was calculated for eight of the 27 cases chosen at random; the mean intrasubject coefficient of variation was less than 1%. We therefore considered a fall of at least 2% to be clinically important in individual patients.

Dichotomous variables were analysed by Fisher's test of exact probability or McNemar's test, where appropriate.[9] Other results were analysed using Student's paired *t* test with a check for order effects. Informed consent was obtained from all parents, and all parts of the trial, including the study using nebulised saline, were approved by the hospital ethical committee.

Results

There was no difference in the time taken to nebulise the salbutamol with the two driving gases. Respiratory rates were similar before each treatment period and did not alter significantly afterwards. The driving gas used did not make any obvious difference to the bronchodilator effect of the nebulised salbutamol when judged by changes in peak expiratory flow rate (table).

Nearly every child had a tachycardia at the outset, with mean heart rates before treatment of 125·9/minute (air) and 122·6/minute (oxygen), p>0·1. During treatment with compressed air, mean heart rate increased (p<0·001) and this increase was sustained after treatment (p<0·01). No such increase occurred during treatment with oxygen (p>0·05), but there was an increase in mean heart rate after treatment (p<0·01). There was no order effect (fig 1).

The figures for arterial oxygen saturation were similar before each treatment, before treatment with air the mean was 92·0% (range 86·9–95·5%) and before treatment with oxygen the mean was 91·9% (range 88·1–94·9%). There were no significant changes in mean arterial oxygen saturation for the group as a whole during or after treatment with compressed air. When the children were given

Table *Changes in respiratory (n=27) and peak expiratory flow rates and nebulisation times when treatment was driven by compressed air or by 100% oxygen*

	Air		*Oxygen*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*
Mean (SD) respiratory rate	31·8 (11·2)	32·7 (10·3)	32·3 (11·7)	31·2 (9·1)
Mean (SD) peak expiratory flow rate (% of predicted)*	57·2 (29·2)	67·3 (28·1)	58·0 (30·3)	70·0 (30·0)
Mean (SD) time on nebuliser (minutes)	9·9 (2·2)		9·7 (2·3)	

*Seven of 19 patients on air and 10 of 20 on oxygen had a rise of >10%

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nebulised salbutamol driven by oxygen. there was a rise in mean arterial oxygen saturation which lasted until the end of the treatment. During the period immediately after treatment, the mean arterial oxygen saturation fell, and stabilisation took up to five minutes. The mean arterial oxygen saturation 5–10, and 10–15, minutes after treatment using oxygen did not differ either from the baseline value or from the mean arterial oxygen saturation after treatment using compressed air (fig 2).

Arterial oxygen saturation fell by at least 2% from the value before treatment in 10 children: seven when compressed air was used, two when oxygen was used, and one with both driving gases. During treatment using compressed air four children had falls of 2–3·5%. In two of these and in a further four children, arterial oxygen saturation was at least 2% below baseline values 5–15 minutes after the end of the treatment. This fall was greater than 4% in three cases, the greatest being 6·[illegible]% to an arterial oxygen saturation of 85·4%. In three cases arterial oxygen saturation fell by more than 2% after nebulised salbutamol driven by 100% oxygen (one had also had a pronounced fall in arterial oxygen saturation when compressed air was used), one child had a drop in arterial oxygen saturation of over 4%.

The 10 children who developed clinically important hypoxaemia did not differ from the others in either pulse or respiratory rate, or peak expiratory flow rate, or arterial oxygen saturation, or other medication, before treatment. Eight of them (including the four whose arterial oxygen saturation fell by more than 4%) were under the age of 7 years, and five fell asleep during or after treatment. Children fell asleep more often when compressed air was used (nine out of 27) than when oxygen was the driving gas (two out of 27); $p<0·05$, McNemar's test.

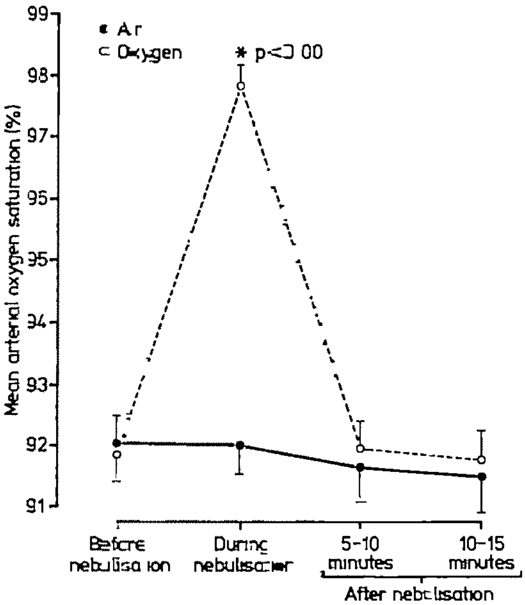

Fig 1 *Mean arterial oxygen saturation in 27 cases before, during, and after nebulised salbutamol driven by compressed air or 100% oxygen. Bars indicate 1 SE.*

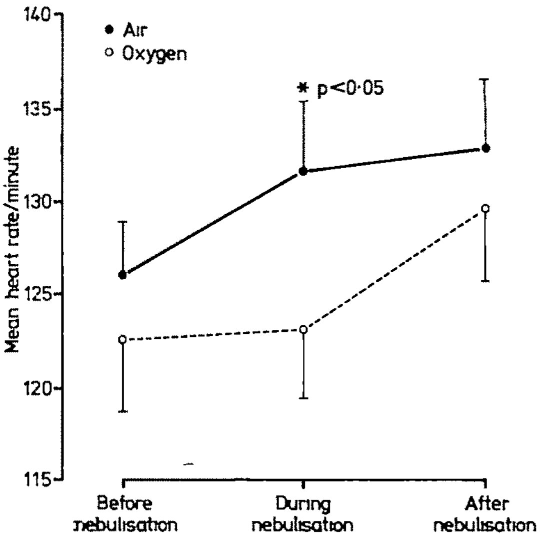

Fig 2 *Mean heart rate in 27 cases before, during, and after nebulised salbutamol driven by compressed air or 100% oxygen Bars indicate 1 SE*

Discussion

Hypoxaemia after treatment with bronchodilators probably reflects a comparatively greater increase in pulmonary perfusion than in ventilation—that is an increase in ventilatory perfusion mismatch. This increase in perfusion may be due to a β-2-adrenergic pulmonary vasodilation effect or a β-1-adrenergic effect that increases cardiac output, or both.[10] The frequency and degree of hypoxaemia that we observed was less than that described in previous studies of salbutamol inhalation in wheezing children. The mean arterial oxygen saturation did not decrease in our group of patients, and arterial oxygen saturation decreased by at least 2% in only 11 of 54 studies. In one study a fall in arterial oxygen saturation of more than 5% in nine of 18 asthmatic children aged 2–15 years was reported.[4] In this study arterial oxygen saturation before treatment was higher and heart rates were lower than in our patients, suggesting that the airways obstruction may not have been as severe. They recorded arterial oxygen saturation at fixed time points so their results would not allow for brief fluctuations in saturation. Also, no mention was made of the quality of the pulse wave forms obtained, and (as has been pointed out recently) artifactual falls in arterial oxygen saturation can result from inadequate waveforms.[8] The pulse oximeter we used (Biox 3700) displays the pulse wave patterns and quantifies the strength of the signal so that values recorded during suboptimal conditions can be disregarded.

The one study of oxygenation in wheezy infants after nebulised salbutamol showed a significant deterioration in the five babies investigated.[6] It was suggested that abnormalities in ventilation perfusion and therefore hypoxaemia might be more likely to occur in infants because they frequently do not dilate their bronchi in response to salbutamol and, indeed, obstruction to the airways may actually increase [11] In our study the children who showed the largest falls in oxygen saturation were among the youngest, but there was no association between fall in arterial oxygen saturation and a poor response to nebulised salbutamol

Giving nebulised salbutamol with oxygen as the driving gas had two potential benefits. Firstly (as one might expect), hypoxaemia did not occur during treatment. Five to 15 minutes after completion of treatment, however, arterial oxygen saturation was no different from that when compressed air was used, and pronounced hypoxaemia still occurred in a few patients. Secondly, the children were less likely to fall asleep when given oxygen with nebulised salbutamol. Drowsiness was noted as an occasional unwanted effect in a survey of the use of home nebulisers,[2] and in our previous study five of 19 children with acute asthma fell asleep after being given nebulised salbutamol driven by compressed air.[5] These five children, and four of the nine children who fell asleep after nebulised treatment using compressed air in our present study, showed a fall in oxygenation. Sleep in chronic adult asthmatics is associated with hypoventilation and a decrease in arterial oxygen saturation.[12] Respiratory rates did not alter in our patients, but we did not measure tidal volume so hypoventilation could be at least partly responsible for the hypoxaemia. In support of this view, the larger number of patients who became hypoxaemic after nebulised salbutamol driven by compressed air can be explained by their sleep state; in those who remained awake the frequency of hypoxaemia was similar after both driving gases. It is not at all clear why treatment using compressed air should be more likely to induce sleep, but it is probably not the noise of the compressor because compressors were not used in our earlier study

The increase in heart rate that occurred during treatment with nebulised salbutamol driven by compressed air did not occur during treatment with nebulised salbutamol driven by oxygen. There was a slight increase in heart rate during treatment with nebulised saline and there was no difference when the nebulised saline was driven by air or oxygen. It is difficult to explain this possible inhibition of the β 1 effect of salbutamol by oxygen, but heart rates rose when oxygen was discontinued.

The recent New Zealand Asthma Mortality Study concluded that in all cases where home nebulisers driven by compressed air were used during the final attack 'the probability that inhalation of β sympathomimetics by nebuliser contributed to death was lower than the probability that death would have occurred without treatment'.[3] It is reassuring that in most of the children we studied nebulised salbutamol driven by compressed air was not associated with hypoxaemia, and when arterial oxygen saturation did fall the changes were comparatively small. On the other hand, hypoxaemia was unpredicatable and although a fall of 2–6% is probably not clinically important when arterial oxygen saturation is above 90%, it would be extremely important if the arterial oxygen saturation before treatment with the nebuliser was less than 85% and on the steep part of the oxygen dissociation curve.

Our observations emphasise the importance of explaining to parents of children with nebulisers at home that when the child has an acute attack of asthma they shoiuld not persist with unsupervised use of the nebuliser. We recommend that they seek medical advice if there is no improvement after one dose of nebulised salbutamol or if it is needed more often than four hourly. Using oxygen as the driving gas conferred only transient benefit, and oxygen needs to be given continuously to children who are extremely hypoxaemic during a severe acute asthmatic attack.

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Airway responsiveness in low birthweight children and their mothers

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SUMMARY In a prospective study on a cohort of 7 year old children of low birth weight (under 2000 g at birth), we observed an increased prevalence of airway responsiveness to histamine compared with a reference population of unselected, local schoolchildren. The airway responsiveness to histamine was significantly related to a history of asthma in first degree relatives (natural parents and siblings) in both groups of children, but not to that of the mothers. There was no increase in the prevalence of maternal asthma, a family history of asthma, or airway responsiveness in the mothers of low birthweight children. We were unable to find evidence to support the hypothesis that maternal smooth muscle irritability (uterine and airway) has a causative role in the premature labour in the mothers and in subsequent bronchial hyper-responsiveness in their prematurely born children.

Increased airway responsiveness to histamine or methacholine has been reported in long term survivors of bronchopulmonary dysplasia[1] and respiratory distress syndrome,[2 3] and after neonatal mechanical ventilation,[4] suggesting that neonatal respiratory illness and its treatment are associated with airway hyper-responsiveness detectable many years later. The importance of such observations is immense as they could imply a much worse prognosis for adult obstructive airway disease than might formerly have been suspected.

Recently bronchial hyper-responsiveness has also been shown in prematurely born children without neonatal respiratory illness.[3 5] Bertrand *et al* have even shown that both the full term siblings and mothers of preterm children have a much greater level of airway responsiveness than control groups.[3] While their study was small and could have suffered from bias, their hypothesis was ingenious: irritability of both uterine and airway smooth muscle of the mothers could act as a common pathway in the aetiology both of premature labour and of bronchial hyper-responsiveness in both mothers and their children (full term and preterm). This hypothesis is supported by the use of selective β adrenergic agents to reduce uterine smooth muscle activity in obstetrics and smooth muscle activity in airway disease. Further supporting evidence comes from the observation that a family history of asthma, of which increased airway responsiveness is an associated manifestation, is commoner in survivors of bronchopulmonary dysplasia[6] and respiratory distress syndrome.[3] The hypothesis of Bertrand *et al* has not been adequately tested.

The reports published so far are all retrospective studies based on small samples of hospital populations, often without adequate control groups. They suffer from potentially severe sampling bias, such that the inferences that can be deduced are limited by their study design. The true prevalence of airway responsiveness in populations of preterm, low birthweight children is not known.

In this paper we report the initial results of lung function tests from a prospective study of a cohort of low birthweight children and a random reference population of schoolchildren of the same age. The study aimed to determine the distribution of airway responsiveness to histamine, the relation between airway responsiveness and maternal or family history of asthma, and the prevalence of airway hyper-responsiveness in mothers of low birthweight children.

Subjects and methods

All infants of birth weight between 500 and 2000 g born in the 12 month period from June 1979 to May 1980, at Hammersmith and Queen Charlotte's Hospitals, were recruited into a long term multidisciplinary follow up study from birth. Perinatal data were recorded soon after discharge from the neonatal unit. Of the 218 survivors in this cohort of 294 live births, one refused to take part in this study, 23 were known to have emigrated, and three were lost to follow up. At 7 years of age (mean (SD) age 7·00 (0·16), range 6·2–7·9 years) 134 children attended the lung function clinic. Of the 57 who did not have lung function tests, 38 lived at a distance (outside the boundaries of Greater London) three had severe mental retardation, and one was in care with the social services department. Comprehensive information was also available on seven members of multiple births whose birth weight was over 2000 g. Although not included in the cohort, they were documented in the same way as their low birthweight twin or triplet.

In the second half of our study, all mothers who accompanied their children to our clinic were invited to take part in the histamine challenge test Out of 37 requests, 36 consented to take part. One mother who was unable to perform reproducible peak flow manoeuvres due to muscle disease did not take part. Thirty five mothers completed the airway response test to histamine.

We also carried out lung function tests and airway response tests to histamine in a reference population of schoolchildren recruited from three schools near to Hammersmith Hospital. All 166 pupils in the third and fourth years whose age was between 6 and 8 years at the time of the school visits were included. Parental consent was sought by sending parents of each child an explanatory letter together with a questionnaire through the class teachers. Twenty two parents did not reply and 16 parents did not give consent. Of the 128 parental consents obtained (77% of the total), two arrived after the whole study had been completed. Three children were absent from school due to illness after having obtained parental consent and three children were not tested because they had active colds. Four children did not consent to the test and the test was discontinued in a further four because of hoarseness and coughing. The airway response test was completed by 112 children in the reference group. Their mean (SD) age was 6·95 (0·43) years (range 6·2–8·0 years).

An identical questionnaire was used to determine the personal and family history of members of the low birthweight cohort and the reference children. The following features of relevance to this study were recorded: personal history of cough and wheeze, asthma or atopic illness, and history of asthma or other atopic illness in parents and siblings. Questionnaires were sometimes incompletely filled and this is reflected in the varying numbers which are reported in the tables.

The tests on low birthweight children were carried out at hospital clinics over the course of one year, whereas the control population of schoolchildren was studied over a period of six weeks in February and March 1987 at their schools

We used the rapid method developed by Yan *et al* to measure airway responsiveness,[7] using handheld DeVilbiss No 40 nebulisers. The histamine solutions at different concentrations were prepared at weekly intervals by serial dilution with saline from a stock solution of 32 mg/ml unbuffered histamine acid phosphate prepared by the pharmacy at Hammersmith Hospital. The histamine solutions used for airway provocation tests were all freshly drawn from these solutions at the beginning of each session. The output of these nebulisers had been assessed and checked before tests were carried out. Peak expiratory flow rate as recorded by the Wright peak flow meter (Airmed) was used to measure changes in airway function.

After being adequately taught the peak flow technique, the children were asked to perform four peak flow manoeuvres to establish within subject reproducibility of peak expiratory flow rate before any aerosol was given After nebulised saline administration to exclude a non-specific airway response to aerosol, the children were given doubling doses of histamine according to the schedule shown in table 1. Sixty seconds after each administration, two recordings of peak expiratory flow rate were obtained, followed immediately by the next dose of histamine. If the difference between the two recordings was greater than 10%, a third attempt was requested The highest value was used in analysis. Increasing doses of histamine were given according to schedule until the fall in peak expiratory flow rate exceeded 20% from the baseline post-saline level or until a maximum cumulative dose of 6 µmol had

Table 1 *Histamine dose schedule*

Dose number	*Histamine solution concentration (mg/ml)*	*No of puffs*	*Cumulative dose (µmol)*
1	2	2	0·07
2	2	4	0·15
3	8	2	0·33
4	8	4	0·7
5	32	2	1·5
6	32	4	3·0
7	32	8	6·0

been given, whichever was the sooner. The children were seated throughout the test.

A dose response curve was constructed by plotting the highest peak expiratory flow rate against the cumulative dose of histamine on a log scale. The cumulative dose of histamine required to cause 20% fall in peak expiratory flow rate from the post-saline level (PD_{20}) was obtained by linear interpolation of the dose-response curve.

During the course of the study, when it became apparent that there were no children with a PD_{20} less than the second dose of histamine in our schedule, the protocol was modified by combining the first and second doses as one single dose (4 mg/ml, three puffs).

The same method was used to measure airway responsiveness in the mothers of low birthweight children and in the reference population of healthy schoolchildren.

Skin prick tests for atopy were carried out in the low birthweight children but not in the control population. Three common allergens—namely, housedust mite, group B grass pollens, and cat fur (Bencard)—were administered together with a control solution. A skin test was considered to be positive if there was a weal of 2 mm or more in diameter to any one of the allergens in the absence of any response to the control solution.

Neonatal history and questionnaires were not analysed until the whole of the study had been completed. The neonatal history of the children was not known at the time of testing.

Statistical analysis of the distributions of airway responsiveness in the two populations of children was done by Mann-Whitney U test. Significance of the association between various factors and the presence of airway responsiveness, and the comparison of the prevalence of these factors in the two populations of children was assessed by the χ^2 test.

Written consent was obtained from the parents of all subjects. The studies were approved by local ethics committees.

Results

Of the 134 children from the low birthweight cohort who attended our clinic, 122 completed the airway response test satisfactorily. Three children were unable to take part in breathing tests at all because of the presence of tracheostomy in one and mental retardation in the other two. A further two were unable to perform reproducible peak flows due to coordination difficulties relating to underlying neurological problems. Two children were unable to produce a peak flow greater than 80 1/minute and one child who had a cold did not take part in the test. Four children refused the airway response test.

The mean (SD) birth weight of the 122 children who completed the airway response test in the cohort was 1472 (348) g (range 730–1990 g), and the mean (SD) gestational age was 31·8 (2·8) weeks (range 27–39 weeks). Eight children were of gestational age 37 weeks or over, but were small for gestational age. Altogether there were 45 small for dates babies (birth weight under 10th centile for gestational age). On the basis of questionnaire reports from parents of the reference schoolchildren there were three preterm children of gestational age between 35 and 36 weeks. None weighed below 2000 g at birth.

A total of 87 (71%) of the low birthweight children had a PD_{20} of 6 μmol or less compared with 48 (43%) children in the control population (table 2). The frequency distribution of the airway response to histamine in both populations was continuous, with that for the low birthweight children significantly shifted to the left compared with the controls (figure). The median for the low birthweight children was around 4 μmol whereas that for

Table 2 *Airway responsiveness to histamine*

Cohort	*PD_{20}* (μmol)*			
	0–1 *No (%)*	*>1–3* *No (%)*	*>3–6* *No (%)*	*>6* *No (%)*
Low birth weight (n=122)	18 (15)	35 (28·5)	34 (28)	35 (28·5)
Reference (n=112)	10 (9)	19 (17)	19 (17)	64 (57)

$\chi^2=18\cdot2$, $p<0\cdot001$

*PD_{20} is the cumulative dose of histamine required to cause 20% fall in peak expiratory flow rate from the post-saline level.

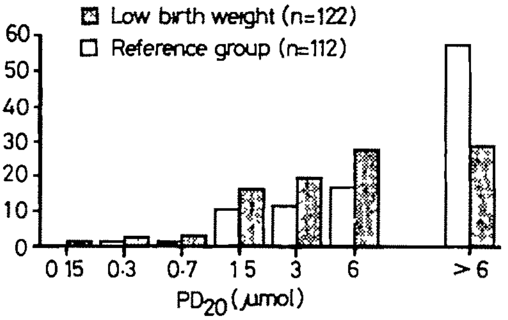

Figure *Frequency distribution of airway responsiveness to histamine in 7 year old low birthweight children and a reference population. The cumulative dose of histamine required to cause 20% fall in peak expiratory flow rate from the post-saline level (PD_{20}) is plotted on a $\log_{10}$ scale.*

the reference population was greater than 6 µmol (Mann Whitney U test $p<0·001$).

Using the same protocol, five of the 35 mothers of low birthweight children (14%) showed a positive airway response to histamine to a maximum cumulative dose of up to 6 µmol. The results of a survey of airway responsiveness to histamine in an adult population carried out by Woolcock *et al*, using the same technique but with a lower maximum cumulative dose of 3·9 µmol, reported a prevalence of 10·5%.[8] At a dose of 3·9 µmol the prevalence of airway responsiveness in the mothers of our low birthweight cohort was almost identical at 8·6%.

There was no significant difference in the prevalence of asthma in the subjects, their mothers, or first degree relatives, between the low birthweight and reference populations of children (table 3). There was a significant association between a personal or a family history of asthma (but not of maternal asthma alone) and increased airway responsiveness in both the low birthweight and reference children (tables 4 and 5). There was also a significant association between positive skin test to common allergens and airway hyper-responsiveness in the low birthweight children ($\chi^2=7·9$; $p<0·005$). Within the low birthweight cohort, the six mothers with asthma did not go more frequently into spontaneous preterm labour than the non-asthmatic mothers.

Table 3 *Prevalence of asthma in study subjects and members of whose family**

Cohort	*Subjects* *No (total)*	*Fathers* *No (total)*	*Mothers* *No (total)*	*Siblings* *No (total)*
Low birth weight	13 (122)	[illegible] (120)	5 (120)	11 (99)
Reference	13 (105)	[illegible] (99)	3 (110)	8 (90)

*Variation in numbers in brackets is due to the presence of multiple births, brothers and sisters at the same school, single parent families, missing data due to unknown state of natural parents, and incompletely filled questionnaires

Table 4 *Relation between personal history of asthma and airway responsiveness to histamine*

Cohort	*Personal history of asthma*	*PD₂₀* (µmol)*		χ^2	*p Value*
		0–3	*>3*		
Low birth weight (n=122)	Yes	10	1	17·1	<0·001
	No	43	68		
Reference (n=105)	Yes	7	5	8·9	<0·005
	No	18	75		

*PD_{20} is the cumulative dose of histamine required to cause 20% fall in peak expiratory flow rate from the post-saline level

Table 5 *Relation between family history of asthma* and airway responsiveness to histamine*

Cohort	*Family history of asthma*	*PD₂₀† (µmol)*		χ^2	*p Value*
		0–3	*>3*		
Low birth weight (n=121)	Yes	12	6	4·5	<0·05
	No	41	62		
Reference (n=99)	Yes	9	9	6·4	<0·025
	No	17	64		

*In natural parents and siblings
†PD_{20} is the cumulative dose of histamine required to cause 20% fall in peak expiratory flow rate from the post-saline level

Discussion

As a result of other selective, retrospective studies, it has been stated that asthma may contribute to the chronic lung disease which sometimes follows intensive care of preterm infants.[6] There are several ways in which an association between asthma and chronic lung disease could come about. A causal relation would be the simplest. Bertrand *et al* provided evidence for an alternative hypothesis by showing that the mothers of preterm infants in general had hyper-responsive airways.[3] They proposed that prematurity and later airway abnormalities were linked by familial smooth muscle hyper-responsiveness: uterine and airway smooth muscle in mothers and airway smooth muscle in their children. In order to confirm their hypothesis, it is essential to show that:

(1) the prevalence of airway responsiveness in low birthweight children is increased compared with a reference population of equivalent age;
(2) the prevalance of airways responsiveness in the mothers of these children is higher than that of the general adult population;
(3) a maternal history of asthma is commoner in the low birthweight children; and
(4) airway responsiveness in these children is particularly related to the maternal history of asthma.

In our study we showed that the prevalence of airway responsiveness was increased in the low birthweight population (71%) compared with that of the reference group (43%). This observation was in accordance with that reported by Bertrand *et al* (77% of the premature children showed a positive response to histamine)[3] and MacLusky *et al* (65% showed a positive response to methacholine).[5] We were, however, unable to show that the prevalence of airway responsiveness in mothers of low birthweight children was greater that that of the general adult population as reported by Woolcock *et al* using the same methodology.[8] On the basis of self administered questionnaires completed by the children's parents, there was no difference between the low birthweight cohort and the reference group in the prevalence of asthma among mothers or other family members (table 3). Finally, we showed that airway responsiveness in children was related to a personal and a family history of asthma in general and not particularly to a maternal history of asthma (tables 4 and 5).

In this prospectively studied cohort of low birthweight children, we found no evidence to support any association between premature labour and maternal airway hyper-responsiveness (and by implication, uterine smooth muscle responsiveness). Moreover, although a family history of asthma was more common in children with increased airway responsiveness, suggesting a familial component in airway responsiveness, this applied to both low birthweight children and to the reference group. The differences between our study and previous observations require explanation

There are inherent dangers in extrapolating results from limited retrospective studies.[3 6] Observations based on small hospital based samples suffer not only from selection bias, but also bias due to willingness of the solicited subjects and their control group to take part in research studies. Consequently the study sample could be biased towards those who had closer hospital or clinic connections or those with more frequent symptoms. Our study cohort was unbiased, age and birthweight specific, and recruited in the neonatal period.

As in any longitudinal study entailing long periods between the time of inception and the time of observation, some loss of follow up is inevitable. Of the original cohort of 218 survivors, we saw 67% of all available survivors in the United Kingdom in our lung function clinic. Of those who did not come to our clinic, 66% lived outside the boundaries of Greater London. There was no significant difference in mean birth weight and gestational age between those who attended lung function clinics and completed the tests (1472 g and 31·8 weeks) and those who did not (1535 g and 31·7 weeks). We nevertheless sent the parents of these children questionnaires identical to those used in our study. Of the 25 replies received out of a total of 57 sent, there was no significant difference in the prevalence of respiratory symptoms or asthma in their families. Their omission is unlikely to have affected our results or conclusions.

It is impossible to find out the airway responsiveness in those low birthweight children who died as infants. We cannot say whether their deaths could have been in any way related to their endogenous airway responsiveness. On the basis of the questionnaire administered to mothers in the neonatal period, neonatal and postneonatal deaths were not associated with an increased prevalence of maternal history of asthma and hay fever

Airway hyper-responsiveness to chemical irritants such as histamine and methacholine is an established feature of childhood asthma.[9] Its presence has been shown to be significantly related to respiratory symptoms based on a conglomeration of positive responses to questions about wheeze, exercise wheeze, and night cough.[10] It has also been observed in children with a variety of chronic airway diseases and many years after acute infantile lung infections.[11] In addition some normal children without any respiratory symptoms may have hyper-responsive airways.[9] Our finding of increased airway responsiveness in low birthweight children was not related to their prematurity, as we were unable to show any direct relation between airway responsiveness and gestational age or birth weight. The possibilities that increased bronchial responsiveness resulted from neonatal intensive care or subsequent environmental factors remain to be tested.

Our findings support a familial component in airway responsiveness in both low birthweight children and schoolchildren in general It is possible that prematurity or neonatal intensive care could in some way enhance the occurrence and persistence of airway responsiveness in low birthweight children. We reject the hypothesis, however, that maternal smooth muscle irritability is a common factor in the aetiology of premature labour in mothers and of bronchial hyper-responsiveness in their children.

We thank the parents and children of our low birthweight cohort for taking part in the study We also thank the staff, parents, and children of East Acton First School, Berrymede Junior School, and Derwentwater Junior School for their help and cooperation in the research, and the Education Department of the London Borough of Ealing for permission to carry out the study on school premises

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Effect of continued feeding of cows' milk on asymptomatic infants with milk protein sensitive enteropathy

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SUMMARY The clinical response and the histological changes in the mucosa of the small bowel in response to continued feeding with cows' milk protein were assessed over a period of 2–6 weeks in 24 infants who had shown histological changes without immediate clinical symptoms after challenge with a diet containing cows' milk protein. Twenty of the 24 infants (83%) thrived well on cows' milk protein. Jejunal biopsy specimens taken six to eight weeks after the initial biopsy showed histological improvement in all 20 infants compared with biopsy specimens taken soon after the challenge, which had shown mucosal damage. The mucosa had returned to normal in 12, was mildly abnormal in seven, and moderately abnormal in one. Corresponding improvements in the activities of mucosal enzymes were seen. In four of the 24 infants (17%) symptoms developed between three and six weeks. Histological examination of the jejunal biopsy specimens showed that mucosal damage had progressed in two, and remained the same in two; moreover, the disaccharidase activities remained depressed. The present study shows that most infants with enteropathy caused by sensitivity to cows' milk protein but without clinical symptoms develop tolerance to the protein and the mucosa returns to normal despite continued feeding with cows' milk protein.

Villous atrophy of the proximal jejunum is a consistent histological finding in infants with enteropathy caused by sensitivity to cows' milk protein after they have been challenged with the protein.[1–4] Some infants with damaged mucosa, however, develop symptoms, and others do not. The symptoms, especially vomiting and diarrhoea, may develop either rapidly (within 48 hours) or slowly (over a period of 2–30 days). Some infants remain asymptomatic despite mucosal damage and continued feeding with cows' milk protein.[3–4] In practice this group is not recognised as being intolerant to cows' milk protein. Hence if one of these infants develops diarrhoea weeks later there is confusion as to the cause of the symptoms and precious time is wasted by exploratory laboratory investigations.

Infants with symptoms following challenge with cows' milk protein need to have the protein eliminated from their diet before they will improve. The dietary management of infants with mucosal damage but without immediate symptoms, however, poses a problem; it is not clear whether they should be maintained on an exclusion diet or should receive a conventional cows' milk formula.

The present study was undertaken to determine the effect of continued feeding of cows' milk protein on the clinical course and the histological state of the jejunal mucosa of infants who sustained small bowel mucosal damage but who did not have early (within 48 hours) clinical symptoms after challenge with cows' milk protein.

Patients and methods

We used the histological criteria for the diagnosis of enteropathy caused by cows' milk protein that we have described previously.[4] A total of 35 infants with diarrhoeal disease thought to be caused by intolerance to cows' milk protein were studied. After appropriate correction of fluid and electrolyte imbalances[5–6] the infants were given a predigested formula feed that did not contain cows' milk protein.[7] The infants were kept under observation until they were feeding well, gaining weight normally, and had normal stools. They were then discharged home, the mothers having been supplied with the appropriate prehydrolysed formulas and instructed not to offer any other milk.

The infants were readmitted six weeks later for challenge studies as previously described.[4] [8] The infant was offered 5 ml of the low lactose cows' milk (AL 110) and if no reaction occurred the volume was doubled hourly for the first four hours, then three hourly until the total fluid requirements had been met. If the infants developed symptoms the challenge was stopped and the infants were given an oral rehydrating solution after which they were given a protein hydrolysate formula.

Jejunal biopsy specimens were taken only after informed consent was obtained from the parents. The biopsy specimens were taken through the mouth just distal to the duodenojejunal flexure with the Watson paediatric capsule immediately before the challenge with cows' milk protein and then 20–24 hours later whether or not symptoms developed. The morphological changes in the mucosa were scored as previously described.[4] [5]

Infants who had histological reactions but no symptoms (group 2), and infants without clinical and histological reactions to the challenge (group 3) were studied further. They were maintained on cows' milk (for example, S-26 (Wyeth)) and two to six weeks later were readmitted for complete clinical assessment and a third biopsy. Four infants in group 2 who had relapsed were given a prehydrolysed formula and then had a further challenge about six weeks later.

Routine laboratory investigations performed on initial admission, before and after the challenge after six weeks of diet free of cows' milk protein, and at the second readmission for the third biopsy two to six weeks later included measurement of haemoglobin concentration, total and differential white cell counts, culture of the stools for bacterial and viral enteropathogens, and microscopic examination of the stool for parasitic infection. The mucosal imprint described by Kamath and Murugasu for the diagnosis of infection by *Giardia lamblia* was also carried out.[9] Mucosal disaccharidases and alkaline phosphatase activities were estimated in the jejunal biopsy specimens as previously described.[10] [11] If diarrhoea occurred during the initial illness or after the challenge the Clinitest method was used to detect secondary sugar intolerance.[12]

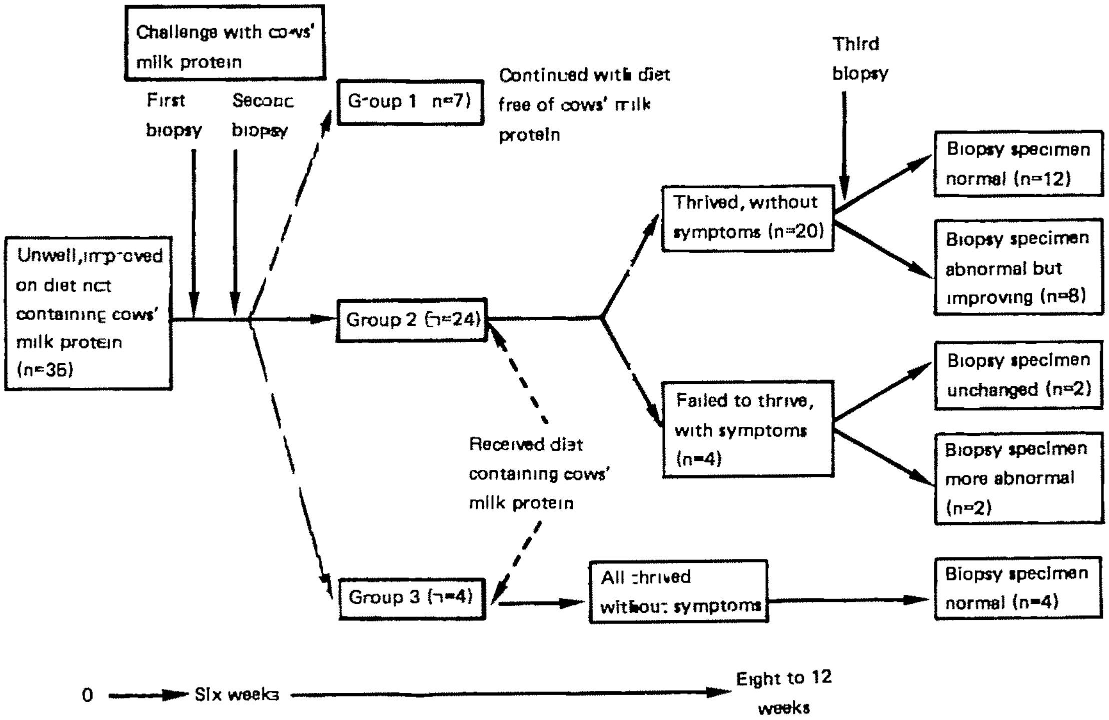
Challenge with cows' milk protein
First biopsy
Second biopsy
Group 1 (n=7)
Continued with diet free of cows' milk protein
Third biopsy
Unwell, improved on diet not containing cows' milk protein (n=35)
Group 2 (n=24)
Thrived, without symptoms (n=20)
Biopsy specimen normal (n=12)
Biopsy specimen abnormal but improving (n=8)
Failed to thrive, with symptoms (n=4)
Biopsy specimen unchanged (n=2)
Biopsy specimen more abnormal (n=2)
Received diet containing cows' milk protein
Group 3 (n=4)
All thrived without symptoms
Biopsy specimen normal (n=4)
0
Six weeks
Eight to 12 weeks

Figure *Flow diagram showing design of study*

Results

The figure summarises the plan and the results of the studies. Thirty five infants were challenged with cows' milk protein From the clinical responses and histological changes in the intestinal mucosa three groups were defined. Group 1 comprised seven infants who developed both clinical and histological signs These infants were not investigated further. Group 2 comprised 24 infants whose biopsy specimens showed histological changes but who had no symptoms, and group 3 comprised four infants who showed no clinical or histological reaction to cows' milk protein. According to the diagnostic criteria groups 1 and 2 had enteropathy caused by cows' milk protein but group 3 did not, and so may be considered as a control group. Follow up studies were based on groups 2 and 3, and the clinical features of these infants at the time of their initial disease are shown in the table.

The infants in groups 2 and 3 were maintained on conventional cows' milk and during follow up 20 (83%) of the 24 infants in group 2 remained well, but four (17%) developed symptoms (figure). The 20 infants who thrived on the formula containing cows' milk protein had a mean (SD) daily weight gain of 28·8 (23·8) g during this period compared with 26·2 (15·3) g during the period when they were having the exclusion diet. The third biopsy specimen of these 20 infants showed varying degrees of histological recovery of the mucosa with normal mucosa in 12, mildly abnormal mucosa in seven, and moderately abnormal mucosa in one.

Table *Demographic and clinical features of 24 infants with positive (group 2) and four infants with negative (group 3) reactions to challenge with cows' milk protein*

	Group 2 (n=24)	*Group 3 (n=4)*
Mean (SD) age (days)	46 (21 3)	83 (61)
Sex male	14	1
female	10	3
Ethnic group Malay	4	0
Chinese	15	1
Indian	5	3
Mean (SD) age at onset of diarrhoea (days)	19 9 (16·3)	79 (62 2)
Mean (SD) duration of diarrhoea (days)	24·3 (20 4)	3 3 (1 5)
Symptoms		
Diarrhoea	24	4
Vomiting	12	1
Dehydration	6	1
Fever	7	1
Anal excoriation	20	3
Thrush	8	0
Abdominal distension	8	0
Eczema	3	0
Anaphylaxis	1	0
Bloody diarrhoea	3	0

The four infants in group 2 who failed to tolerate cows' milk developed diarrhoea, eczema, and persistent rhinitis, and failed to thrive. The histological appearance of the third biopsy in these infants showed that the mucosal damage had progressed in two, and remained unchanged in the other two. Interestingly, one of the four infants thrived on the formula containing cows' milk protein for six weeks with a mean daily weight gain of 10 g before developing diarrhoea and vomiting The four infants required protein hydrolysate substitutes before they improved clinically. A fourth biopsy about six weeks later of these four infants showed normal histological appearances of the intestinal mucosa, but a further challenge with cows' milk protein at this time produced symptoms immediately and these were associated with severe mucosal damage unlike that seen after the first challenge when the onset of the symptoms had been delayed.

The infants in group 3 remained well and gained weight on conventional cows' milk with a mean (SD) daily weight gain of 29 (1·7) g, which compared favourably with the daily gain of 29·3 (4) g during the period when they received the exclusion diet following their initial illnesses.

The mucosal disaccharidase activities were estimated in biopsy specimens obtained before and 24 hours after challenge with cows' milk protein, and two to six weeks after the challenge on a conventional milk diet in 13 infants in group 2. Compared with the prechallenge estimations the postchallenge values of lactase, sucrase, and maltase decreased by about 37%. These values increased, however, by 37–109% after the second challenge two to six weeks later when the infants were on a conventional milk diet compared with the initial values

Discussion

There is no satisfactory reason why infants with enteropathy caused by cows' milk protein, even those with moderately severe villous atrophy, remained asymptomatic and thrived well on cows' milk protein while others developed symptoms and required exclusion diets. There is also no satisfactory reason why some infants with mucosal damage reacted rapidly to challenge with cows' milk protein while others reacted only slowly. Similar observations have been recorded in studies on enteropathy caused by cows' milk protein, soy protein, and gluten.[3 4 8 13]

Factors such as intercurrent infection, secondary intolerance to sugar, antigenicity of cows' milk protein, and the extent and severity of mucosal damage, certainly influence the nature, severity, and onset of symptoms in infants with enteropathy caused by sensitivity to food.[14] The current study not only confirms earlier observations of depressed mucosal enzyme activity in damaged mucosa[8 10 11] but in addition, shows unexpected and interesting increased enzyme activity in the second follow up biopsy specimen taken about one month after the challenge compared with the enzyme activity in the mucosa before the challenge. It is possible that the increased enzyme activities were associated with induction of these enzymes by the conventional infant formula feeds containing lactose that they were receiving during this period compared with the prehydrolysed formula that they received during the period before the first biopsy. There is strong evidence that sucrase is induced by diet[15 16] but lactase appears not to be in humans[17 18] although it is in rats[19 20] On the other hand, the raised enzyme activities may merely reflect the repair of the structural damage after challenge with cows' milk protein.

Our observations suggest that both the digestive potential and the immunological integrity of the mucosa have important roles in excluding antigens from susceptible tissues Naturally the capacity of the villi to recover rapidly would enhance the immunodigestive functions and therefore directly assist in excluding the offending antigens by rapid proteolytic breakdown to non-antigenic peptides. This physiological measurement is difficult to assess and probably relates to the functional maturity of the small bowel mucosa Even so, it is difficult to explain why an infant given as little as 5 ml of cows' milk showed within 30 minutes of ingestion both violent clinical and histological reactions, whereas another infant showed only a histological reaction after consuming more than a litre of the milk. One explanation may lie in the nature and type of the immune mechanisms in the pathogenesis of mucosal damage induced by cows' milk protein.[14 21–26] Moreover, it is possible that with the strengthening of the suppressor pathway the immune responses to the food proteins are modified. Another possible explanation may be the recovery potential of the mucosa under adverse conditions.

The development of clinical tolerance and histological repair despite the continued feeding of cows' milk protein to infants with enteropathy caused by cows' milk protein but without symptoms suggests that mechanisms for spontaneous self repair of the small bowel mucosa in these infants remained effective even under adverse conditions. The factors that promote or impair healing of the mucosa, however, remain unclear. Further studies on the complementary roles of the digestive and the immune functions in the gut in excluding antigens are necessary.

The present study showed that most infants with enteropathy caused by cows' milk protein but without symptoms thrive well with satisfactory mucosal recovery when maintained on cows' milk. Furthermore, though the jejunal biopsy was useful in diagnosing the enteropathy, it had limited prognostic value, particularly in infants with histological damage without symptoms after challenge with cows' milk protein

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The teenage coeliac: follow up study of 102 patients

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SUMMARY Over a 10 year period a total of 102 teenage patients with coeliac disease were assessed on transfer from paediatric hospitals to an adult clinic. Fifty seven patients said they were on a strict gluten free diet; 36 were semistrict, and nine admitted to eating a normal diet. Jejunal mucosal abnormalities, however, suggested that many patients on the 'strict' diet were actually consuming gluten. All patients were well with biochemical parameters within the normal range. Height percentiles were not significantly different from the normal population but patients, as a group, were significantly lighter.

The clinical presentation of coeliac disease in childhood and adult life has been well documented. Little is known, however, about the progress of children with coeliac disease in the 'teenage' years. Three previous studies have assessed the wellbeing of patients after growth into young adult life.[1-3] On the basis of clinical and laboratory findings, these groups came to the conclusion that a strict gluten free diet should be recommended for life. Compliance with this strict diet is, however, very variable.[4 5]

The aim of this study was twofold. Firstly, we wished to assess the general wellbeing of teenage patients with coeliac disease and to correlate this with the strictness of their gluten free diet. Secondly, we wondered whether the feeding patterns, ethnic origins, or age at diagnosis had changed from those previously quoted for children with coeliac disease.

Patients and methods

A total of 102 patients (56 females, 46 males) aged 12–20 years with coeliac disease were assessed in the coeliac clinic during the years 1974–84. Most of the patients were referred for their continued follow up in adult life by two centres: 47 patients came from the Hospital for Sick Children and 38 from Queen Elizabeth Hospital for Children; 17 patients came from other centres or from general practitioners.

At transfer all patients were seen by one of us (PK). All had a detailed case history taken. A clinical examination was performed with the documentation of their height and weight on percentile charts. All patients were offered blood tests but some refused on the basis that they felt very well. Most patients, however, had a full blood count, liver function tests, and measurements of serum B_{12} and red cell folate performed. Patients were asked to assess their own diet as strict (no gluten intake), semistrict (consuming several items of gluten per week), or normal (no gluten restriction at all); in some patients a formal dietary check was conducted by a dietitian.

Patients were offered a jejunal biopsy either for a gluten challenge (if this had not been performed) or if a biopsy had not been performed for two years or more. Forty four patients agreed to have a jejunal biopsy. Biopsies were taken at the duodenojejunal junction under fluoroscopic control using a Crosby capsule. Villous heights were measured using an eye piece micrometer. An average count of 10 villi on each specimen was made under ×10 magnification.

Results

All patients were well and leading normal healthy lives. One patient, however, although otherwise well, had symptoms of the irritable bowel syndrome that were bad enough to necessitate further radiological studies of her bowel. There were no other symptoms referable to the gastrointestinal tract apart from the 'occasional' attack of diarrhoea or abdominal pain which was passed off, by parents and patients alike, as part of normal life.

The patients' assessment of the strictness of their diet before transfer to an adult clinic was as follows: those who considered their diet to be strict, 57; semistrict, 36; and normal, nine. After follow up in an adult clinic for more than one year the numbers were: strict, 45; semistrict, 46; and normal, 11. The gluten equivalent (assessed by the dietitian) was: strict, no gluten; semistrict, 2·5–10 g gluten; and normal, >10 g gluten. In a few cases the actual diet eaten by patients was only admitted to after the parents had left the consulting room.

Although most patients were very well informed about their diets a few children, although ostensibly on a strict diet, had no idea about the gluten content of various foods when repeatedly questioned (with their mothers) by the dietitian. Nevertheless, there was a good correlation ($r=0\cdot888$) and no significant difference ($p=>0\cdot22$) between the dietitian and patients own view of the strictness of the diet. This was not surprising as the former could only assess the diet on the information given by the patient. Most patients appeared to have self-selected their diets; almost all patients on the 'strict' diet found it no problem while those on the normal diet found a strict diet difficult to adhere to for practical or social reasons (For example, the marriage prospects for an Asian girl were reduced if she was known to be on a diet) In some cases, although patients said they had gluten free school lunches and gluten free food at home, when they went out with their friends at 'break-time' they ate hamburgers, rolls, biscuits, cakes, etc.

Patients appeared not to have any major problem over having gluten free food at school; most patients took gluten free packed lunches while some schools actually provided gluten free meals. One patient at boarding school had a term's worth of gluten free bread stored in a freezer at school.

The assessment of the diet after follow up in an adult clinic for more than one year (see above) was made to see if the transfer from a paediatric to an adult centre made children less conscientious over their diets. Only a few teenagers had become less strict during their follow up in an adult clinic. It should be emphasised that all children were on regular follow up and the policy in both paediatric and adult centres was to advise patients to adhere to a strict gluten free diet.

Of the ethnic origins of the patients, 23 had first degree relatives with Irish origins. The remainder were white but not Irish; two were of Asian origin.

When the feeding patterns in infancy were examined, 36 of 69 patients were breast fed. The weaning age varied from 3 weeks to 1 year of age with an average of 3·76 months.

Fifty one patients were diagnosed in the first 2 years of life and 26 over 10 years of age. Symptoms were noticed from a few weeks to many months after weaning (mean=2·8 months). There was a delay in diagnosis from the onset of symptoms of up to 14 years, with 34 patients being diagnosed within two months of onset of symptoms, but 12 had had symptoms for five years or more. There was no correlation between the actual age of weaning and the presentation of symptoms in those patients diagnosed at an older age.

Associated and past diseases are shown in the table. Twelve of the 102 patients had atopic illnesses: asthma (n=3), eczema (n=6), and hayfever (n=3). This incidence is the same as that seen in the general population and there was no correlation with the feeding patterns in infancy. Twenty six patients had first degree relatives with atopic illnesses and of these, 10 had more than one first degree relative with atopy.

PERCENTILES AT TRANSFER TO ST BARTHOLOMEW'S HOSPITAL

There were eight patients out of 87 who were below the 3rd percentile for weight (five female, three male) and six of these were on 'strict' gluten free diets. Of these six, three had presented over the age of 10 years with shortness of stature; one patient had developed thyrotoxicosis and one had diabetes mellitus and asthma, but had reached puberty at transfer. One further patient reached puberty within a few months of transfer. Analyses and comparison with the general population distribution showed that all patients as a group were significantly lighter ($p<0\cdot01$; see fig 1).

There were six out of 70 patients who were below the 3rd centile for height (four female, two male); five of these were on a strict gluten free diet. Again three patients were those who had presented over the age of 10 years with shortness in stature and one patient had diabetes mellitus and asthma. Five had

Table *No of associated and past illnesses in teenagers with coeliac disease*

Disease	*No*
Thyroid disease	2
Diabetes mellitus	1
Rheumatoid arthritis	1
Glomerular nephritis + chronic active hepatitis	1
Idiopathic pulmonary haemosiderosis	1
Sacroileitis	1
Non-specific joint pains	3
Asthma	3
Eczema	6
Hay fever	3
Undescended testes	2
Pyloric stenosis	1
Epilepsy	1
Renal colic	1
Psoriasis	2
Pancreatic insufficiency	1
Hernias	4

reached puberty at transfer. On completion of growth all six remained below the 3rd centile. There was no significant difference in height centiles compared with the normal population distributions (p=>0·22; fig 2).

LABORATORY DATA

Haematology

Three out of 95 patients (all female) had haemoglobin concentrations that were less than the lower range of normal females (115 g/l). Two of these patients were on a 'strict' diet All three had started their periods but had no history of menorrhagia. Six out of 73 had abnormal red cell folate concentrations that were below 363 nmol/l: one with a concentration of 265 nmol/l and the remaining five between 283–333 nmol/l; two of these patients stated they were on a 'strict' gluten free diet.

One of 81 patients had a serum B_{12} concentration of 107 pmol/l (normal >150 pmol/l). This patient admitted to occasional gluten intake. A whole body B_{12} absorption test showed a normal absorption of 80% in this patient. No cause was found for the low serum B_{12} concentration; this was repeated a year later and was within the normal range.

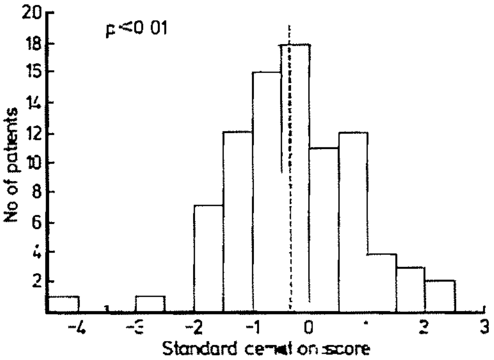

Fig 1 *Weight percentiles at transfer to adult clinic in 87 patients. The dotted line is the median.*

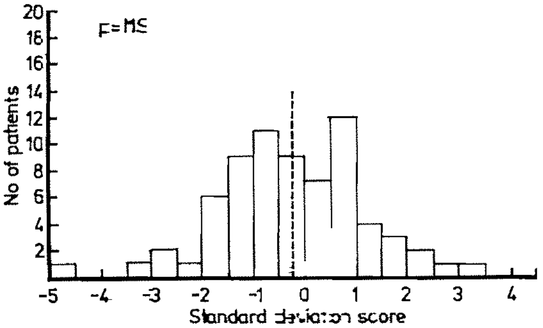

Fig 2 *Height percentiles at transfer to adult clinic in 70 patients. The dotted line is the median.*

Biochemistry

Serum protein and calcium concentrations were within the normal range of our laboratories in 80 patients. One patient had an albumin of 3·4 g/l (normal >3·5 g/l), and although she said she was on a 'strict' diet, the jejunal biopsy specimen was flat. Alkaline phosphatase concentrations were variable and raised above the normal of 120 IU/l in 26 of 78 patients This was compatible with their age and growth.

Appearance of jejunal mucosa

The villus heights of 44 patients are shown in fig 3. Seventeen patients had gross abnormality of villus heights of below 200 µm; of these five claimed to be on a strict gluten free diet and seven were on a semistrict diet. All patients on normal diets had abnormal biopsy specimens.

Discussion

This study shows that all teenagers with coeliac

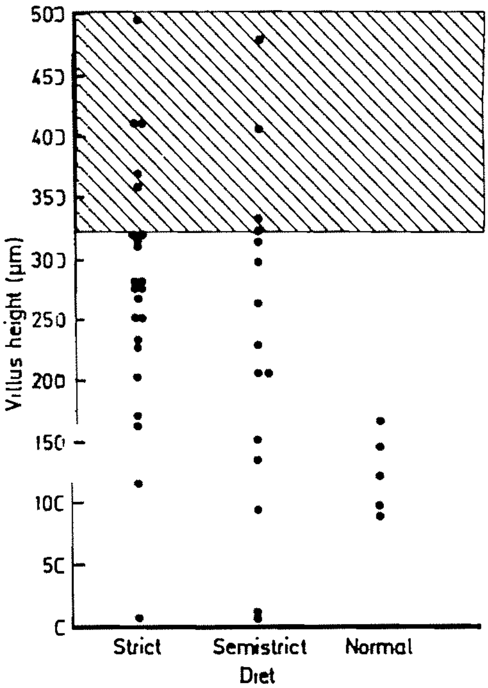

Fig 3 *Villus heights of jejunal mucosa in 44 patients at transfer to adult clinic. Patients are divided into groups on a strict gluten free diet, a semistrict diet and those on a normal diet. The hatched area shows the normal range*

disease were clinically asymptomatic and leading normal healthy lives. Only 57 of the patients, however, were keeping to a strict gluten free diet and nine even admitted to being on a normal diet. Abnormalities of the jejunal mucosa, however, suggested that many more patients were consuming gluten despite being on a 'strict' diet. Although it is possible that these abnormalities of villous height might have been due to a factor other than gluten, four of the five patients in the strict group previously had had a positive gluten challenge (that is, jejunal mucosal deterioration on gluten reintroduction). Laboratory data showed a few abnormalities but all of these were minimal. The red cell folate concentration, measured by the microbiological method, is usually considered to be a good index of untreated coeliac disease. In this series only six of the 73 patients tested had low red cell folate concentrations, suggesting that 'the low gluten diet' that these patients were consuming caused mucosal abnormalities that were insufficient to affect the absorption of nutrients. In contrast, Weir and Hourihane found the concentration of serum folate was the best single measure of whether a patient was maintaining a strict gluten diet, but the number of patients reported were small [5]

Our results are in accord with Jackson *et al* who found that 40% of 50 children were not on a strict gluten free diet.[4] Formal gluten challenge studies have shown that patients often do not develop symptoms on the reintroduction of gluten. Six of 27 children were asymptomatic in a study by Walker-Smith *et al*,[6] and two thirds of teenage and adult patients also remained well, despite jejunal morphological deterioration in another study using long term gluten challenge.[7] Visakorpi showed that it may take many years for children to relapse.[8]

Analysis of the height and weight percentiles showed that although there was no significant difference in height when compared with the normal population distribution, patients with coeliac disease were significantly lighter than their age and sex matched controls. However, we were unable to correlate the strictness of their diet with either the height or the weight centiles that they achieved. Three patients had presented with shortness of stature and were not diagnosed until after the age of 10 years—that is, they were too old for catch up growth to occur.

There was no difference in the feeding patterns in infancy of patients when compared with those seen in the general population. The patterns of breast feeding and weaning age were the same as those seen in the general population in the 1960s and 1970s. This suggests that feeding patterns in infancy had no effect on the presentation of coeliac disease.

The age at diagnosis of our patients was very variable Sixty one patients were diagnosed in the first 2 years of life, but 26 were diagnosed at 10 years and over. Although those diagnosed in the first 2 years became symptomatic soon after weaning there was no correlation between the age of weaning and the presentation of the symptoms in those diagnosed at an older age. About 50% of this older group had, in fact, first presented to the adult clinic The delay in diagnosis was again extremely variable but a third of patients were diagnosed within two months of the onset of their symptoms.

The associated and past diseases showed no increased incidence of any particular condition We could not relate our atopic patients with patterns in breast feeding or bottle feeding, but the numbers are small.

There have been four previous studies documenting the follow up of patients originally diagnosed in childhood Mortimer *et al* followed up 10 adult patients in whom the diagnosis had been made in childhood 18 to 38 years earlier.[3] Nine had a flattened jejunal mucosa but despite this two were asymptomatic. Sheldon in 1969 followed 57 patients (aged 16–27 years) at the Hospital for Sick Children who were originally diagnosed in childhood and treated with two year courses of gluten free diet.[1] He found that on a normal diet 13 patients had relapsed but 44 patients remained extremely well. Of these 44, 19 had low serum folate concentrations, 11 had low serum iron, and six were short. On the basis of this he suggested that a lifelong gluten free diet should be the treatment for these patients. Two years later Young and Pringle, at Queen Elizabeth Hospital for Children, followed up 44 patients diagnosed in childhood after eight to 19 years.[2] The 20 patients on a gluten free diet were well; however, of the 24 on a normal diet only five were well. The remaining 19 of these patients had 'diarrhoea relapses' and five were anaemic Again these authors suggested that a lifelong gluten free diet should be recommended treatment for coeliac disease. Weir and Hourihane followed up 10 patients for four to six years; five patients did not persist with a gluten free diet and although their jejunal biopsies were abnormal, they had no abnormalities on laboratory investigation.[5]

There is no doubt that a gluten free diet is beneficial to patients with coeliac disease. Despite a policy of advocating a strict gluten free diet with regular checks at outpatient follow up, however, our study has shown that many of our patients were not strictly adhering to a gluten free diet, yet all were asymptomatic. Recently, the concept of the permanence of gluten sensitivity in patients with coeliac disease has been challenged. Schmitz *et al* have continued a normal diet in children with confirmed coeliac disease and have shown that the jejunal mucosa actually improved on this diet.[9] Shmerling and Franckx delineated a group (6·6%) of their patients who did not relapse and showed no alteration of the intestinal mucosa after stopping their gluten free diet for at least 2·4 years.[10] These studies put the current definition of coeliac disease into question.

In our study patients remained well despite gluten ingestion. As they were lighter in weight as a group, however, it could be argued that they should keep to a strict gluten free diet. Nevertheless, many patients will 'cheat' and will continue consuming gluten in their diets. It is possible that the actual amount of gluten ingested may be the relevant factor in producing symptoms, whereby small amounts are well tolerated. The fact that children and adolescents may take much longer to relapse has been shown in previous studies[7 8 11] and it is possible that some of our patients may develop symptoms in the future. We would therefore recommend that these patients are followed up regularly with blood tests to detect occult nutritional deficiencies.

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Vitamin B_{12} deficiency in a breast fed infant

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SUMMARY We report the case of a 5 month old breast fed infant who presented with a history of vomiting, pallor, and failure to thrive. Investigations showed severe nutritional vitamin B_{12} deficiency with a megaloblastic pancytopenia. This deficiency was due to low vitamin B_{12} concentrations in the maternal breast milk, and subsequent investigations showed maternal pernicious anaemia. Treatment of the infant with vitamin B_{12} resulted in a rapid clinical and haematological improvement. This case represents an unusual presentation of pernicious anaemia.

Dietary vitamin B_{12} deficiency in infancy is rare, and most reported cases are breast fed infants of mothers who themselves are deficient in vitamin B_{12}, usually on the basis of deficient (particularly vegetarian) diets[1–4] The development of haematologic, neurologic, and metabolic abnormalities in the breast fed offspring of these mothers is usually the presenting feature of the maternal deficiency, which itself may be mild. The case reported here is that of a breast fed infant whose vitamin B_{12} deficiency presented as vomiting, failure to thrive, and megaloblastic pancytopenia at 5–6 months of age. Although maternal serum vitamin B_{12} concentrations and blood film were normal, concentrations of vitamin B_{12} in the breast milk were very low Subsequent studies showed maternal vitamin B_{12} deficiency due to subclinical pernicious anaemia. Three similar cases, two of whom had prominent neurologic abnormalities, have been reported.[5–7]

Case report

A girl, the first born infant of healthy unrelated parents (birth weight 3080 g), was exclusively breast fed and maintained the 25–50th weight percentile until 3–4 months of age when vomiting became a problem This did not respond to the introduction of solids and in the three months before admission she gained only 250 g. Pallor was first noted by her local physician at 5 months of age, and anaemia was diagnosed (haemoglobin concentration 74 g/l). Treatment with oral iron was without effect, and at the time of her referral to the Adelaide Children's Hospital a complete blood count showed pancytopenia with a haemoglobin of 70 g/l, white cell count $7{\cdot}5\times10^9$/l, absolute neutrophil count 530×10^6/l, and platelets 55×10^9/l.

On admission, she was found to be a pale placid infant, with a weight of 5640 g (<3rd percentile), length 66 cm (10th–25th percentile), and head circumference 43 cm (10th percentile). There was no lymphadenopathy and no organomegaly. Neurodevelopmental assessment was consistent with postnatal age, and maternal dietary history was normal. Subsequent investigations of mother and infant are shown in the table.

Table *Results of investigations on infant and mother*

Investigation	*Infant*	*Mother*
Haemoglobin (g/l)	52	136
White cell count ($\times10^9$/l)	3·1	6·6
Absolute neutrophil count ($\times10^6$/l)	400	4550
Platelet count ($\times10^9$/l)	46	>200
Serum vitamin B_{12} (pmol/l)*	<37	273
Serum folate (nmol/l)†	49	9–8
Breast milk vitamin B_{12} (pmol/l)‡	—	44·3
Schilling test	Normal	Abnormal
Barium meal and follow through	Normal	Not tested
Gastric parietal cell antibody	Negative	Positive +
Thyroid cytoplasmic antibody	Not tested	Positive ++
Intrinsic factor antibody	Negative	Positive +++
Free thyroxine index§	Not tested	55
Thyroid stimulating hormone (IU/l)‖	Not tested	126

*Serum vitamin B_{12} normal range=221–885 pmol/l
†Serum folate normal range=6·8–47·7 nmol/l
‡Breast milk vitamin B_{12} normal range=207–1549
§Free thyroxine index normal range 75–150
‖Thyroid stimulating hormone normal result <10 IU/l

The infant's blood film showed appreciable poikilocytosis and anisocytosis with macrocytic changes. The reticulocyte count was 1·4% and there were two nucleated red cells per 100 white cells. Occasional myelocytes and metamyelocytes were seen. A bone marrow biopsy specimen showed appreciable megaloblastic changes with considerable disparity between nuclear and cytoplasmic development in all cell lines, and there was a myeloid: erythroid ratio of 2:1. The low serum vitamin B_{12} concentrations prompted further studies in the infant, including a Schilling test and gastric acid secretion studies all of which gave normal results.

Breast milk vitamin B_{12} concentrations were determined using the same competitive protein binding assay used to determine serum vitamin B_{12} concentrations. Although the validity of this assay system for breast milk B_{12} was not determined, the concentration of 44·3 pmol/l was considerably lower than concentrations determined in our laboratories, using the same assay system, on breast milk samples from healthy lactating women (206·6–1549·4 pmol/l).[4] Also, the concentration of 44·3 pmol/l is low compared with other published normal ranges of breast milk vitamin B_{12} determined by other methods.[8 9] Overall, the low breast milk vitamin B_{12} concentrations suggested subclinical maternal vitamin B_{12} deficiency, and subsequent investigations showed classical (Addisonian) pernicious anaemia and hypothyroidism.

The infant was transfused and vitamin B_{12} (250 μg) was administered as part of her Schilling test. Serial blood counts showed a rapid improvement in neutrophil and platelet counts (see figure). Vomiting stopped coincident with the administration of vitamin B_{12}, and a considerable 'character' change, manifested by increased activity and responsiveness, was noted in the child by both parents and hospital staff. The mother was treated with thyroxine and parenteral vitamin B_{12}. Follow up of the infant at 12 and 18 months showed a clinically normal child with normal haematology and serum vitamin B_{12} concentrations. Now, at 8 years of age she is functioning normally in an age appropriate school setting.

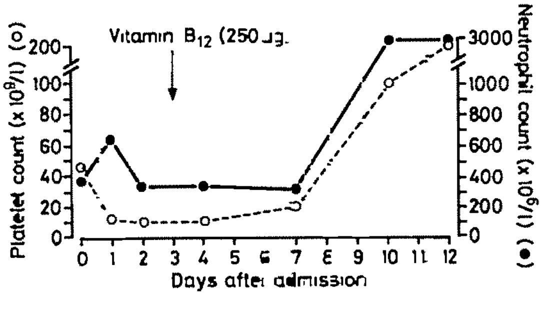

Figure *Neutrophil and platelet counts before and after treatment with 250 μg vitamin B_{12}.*

Discussion

The estimated vitamin B_{12} requirements of the growing infant are 0·06–0·10 μg/day and the normal neonatal vitamin B_{12} stores are of the order of 20–25 μg.[10] Therefore the normal newborn infant has sufficient vitamin B_{12} stores to last for six to eight months, even in the presence of inadequate dietary intake or defective vitamin B_{12} absorption.[10] On the other hand, the vitamin B_{12} stores of the infant of a deficient mother may be as low as 2–5 μg[10] and although normal breast milk has considerable vitamin B_{12},[8 9] the vitamin B_{12} content of the breast milk of deficient mothers is low, as shown by this and other cases.[1–7] Overall, the vitamin B_{12} state of the breast fed infant of a vitamin B_{12} deficient mother is precarious, with marginal stores being aggravated by inadequate dietary intake.

In the present case the maternal complete blood picture and serum vitamin B_{12} concentration were normal. The low breast milk vitamin B_{12} concentration was the only clue to the mother's aberrant vitamin B_{12} state. A similar situation has been described in one other case.[2]

Based on the estimated daily requirements presented above, adequate vitamin B_{12} intake with a breast milk B_{12} concentration of 44·3 pmol/l would require an intake of 1–1½ litres of milk per day. While this would appear achievable, we speculate that the onset of vomiting at 3 months of age in the present case was critical in limiting vitamin B_{12} deficiency. Also, as discussed below, the vomiting itself may have been caused by vitamin B_{12} deficiency. Alternatively, because our normal range for breast milk vitamin B_{12} is considerably higher than other published normal ranges,[8 9] it is possible that our assay method may have overestimated breast milk vitamin B_{12} and that inadequate intake was present from an early age.

The clinical features of vitamin B_{12} deficiency in infancy are predominantly neurologic and haematologic. Neurologic features include an acquired movement disorder, developmental regression, torpor, and even coma.[1–4 6 7] The appreciable character change noted in our patient after the administration of vitamin B_{12} suggests that her placidity on presentation was an early neurologic feature. Other case reports,[6 7] including one from this institution,[4] have reported long term developmental and neurologic sequelae of vitamin B_{12} deficiency in infancy. In general, such sequelae seem to be associated with profound neurologic abnormalities at the time of presentation and presumably the absence of such abnormalities in the present case may explain the good long term outcome.

The haematologic features of vitamin B_{12} deficiency—namely, a megaloblastic pancytopenia—were well illustrated in our case. Other reported features such as mild hepatosplenomegaly, diarrhoea, and a curious palmar pigmentation appear variable, and were not seen in our patient. Vomiting has not been reported previously in association with vitamin B_{12} deficiency in infancy, but was the presenting complaint in our case. The absence of any structural cause, and the prompt resolution of vomiting coincident with the administration of vitamin B_{12} suggest that the vomiting was a symptom of the vitamin B_{12} deficiency.

Three other cases of occult maternal pernicious anaemia presenting as symptomatic vitamin B_{12} deficiency in a breast fed child have been reported.[5–7] Haematologic features were prominent in the case described by Lampkin *et al*,[5] while developmental regression was the presenting complaint in the case of Sadowitz *et al*,[6] and obtundation with hypothermia was seen in the case of Johnson and Roloff.[7]

In summary, a case of vitamin B_{12} deficiency in the breast fed infant of a mother with occult pernicious anaemia is presented. Vomiting and a megaloblastic pancytopenia were features of the infant's presentation. A low breast milk vitamin B_{12} concentration was the only clue to the maternal deficiency. This case serves to emphasise that vitamin B_{12} deficiency presenting at less than 6 months of age is almost exclusively seen in breast fed infants of vitamin B_{12} deficient mothers. In the absence of a deficient maternal diet (particularly a strict vegetarian diet), occult pernicious anaemia should be considered as the reason for the maternal deficiency

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Recurrence incidence of sudden infant death syndrome

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SUMMARY The incidence of sudden infant death syndrome (SIDS) between birth and 2 years of age in South Australia was found to be 2·1/1000 live births. The incidence in previous siblings was 10 times that expected, in second degree relatives five times, and in third degree relatives four times that expected for the community. The minimum incidence in the next subsequent sibling was five times that expected. Except for one family in which both twins died during the same night, the surviving twin has never died (23 infants) The incidence of SIDS in adopted infants was similar to the incidence in natural born infants. Families in which two or more siblings died from SIDS differed from families in which only one infant died from SIDS in several ways. More infants were over 12 months old, and the mothers had an increased incidence of previous miscarriage and threatened miscarriage during the pregnancy with the infant who died. In one family both infants had bronchomalacia, and two families were severely socially deprived.

For most families (92%) in which an infant died from SIDS the risk of recurrence is small (less that twice the expected risk). We have identified a small subgroup (8%) with a significantly increased risk of recurrence.

The sudden infant death syndrome (SIDS) is the death of an infant unexpected by history, and unexplained after thorough necropsy. The incidence in South Australia between 0 and 730 days during the last 15 years was 2·1/1000 live births, between 2 weeks and 2 years it was 2·0/1000, between 1 week and 1 year 1·9/1000, and between 1 month and 1 year 1·8/1000 live births.

Sudden unexpected infant death in siblings was reported by Platerus[1] in 1614, and in cousins by Cheever[2] in 1863. The incidence among previous siblings has been reported as 10 times that expected.[3 4] The incidence in all subsequent siblings was reported as 2·1%, and in the next subsequent sibling as 1·9% by Peterson,[5] and the incidence in all subsequent siblings as 3·7 times and the next subsequent sibling as 4·4 times the community incidence in Norway.[6] Emery described 12 families with two or more cot deaths.[7]

Subjects and methods

FAMILY HISTORY CONTROL SERIES

Between January 1973 and December 1978 one or both the authors visited the homes of 198 infants who died suddenly and unexpectedly, usually within 24 hours of the infant being found dead, to interview and counsel the parents. One hundred and eighty seven of these infants died from SIDS As a result of these interviews it seemed that in some of the families there was a higher incidence of sudden unexplained death in infancy than would be expected. In an attempt to verify this impression a controlled series was undertaken (table 1).

Permission was granted by the Kindergarten Union to ask the parents of kindergarten children to participate in the study. Using the child at kindergarten as the index case, the mother was asked to complete a questionnaire in which she provided information about first, second, and third degree relatives of the child. A similar questionnaire was sent to the parents of the previous 60 children who had had SIDS. Information was sought about the total number of first, second, and third degree relatives, and about all deaths occurring between birth and 2 years, with the age at death and cause of death if known.

Because some of the relatives included in the questionnaire would have died before SIDS was classified as a disease, there was a certain degree of subjectivity as to whether the death should be classified as SIDS. All cases diagnosed as 'silent

Table 1 *Infant mortality in first, second, and third degree relatives of infants who died from SIDS compared with infants who died from other causes*

Relative (degree)	*Infants who died from SIDS (n=60)*			*Infants who died from other causes (n=53)*		
	No who died from SIDS	*No who died from other causes*	*Total No of relatives*	*No who died from SIDS*	*No who died from other causes*	*Total No of relatives*
First	3	1	172	0	0	156
Second	6	6	747	1	6	446
Third	13	17	1234	2	17	1519
Total No	23	24	2153	3	23	2121
Rate/1000	10·2	11·1		1·4	10·8	

pneumonia', 'overwhelming infection', and 'suffocation' were included as SIDS. Where possible the relatives who remembered the death were interviewed and if the child died suddenly and unexpectedly at home without apparently being ill, and was between 1 and 6 months old, this was considered to be SIDS. The same criteria were applied to deaths in both groups. After this study it was decided to continue collecting family histories from families in which a death from SIDS had occurred. Because of the difficulty of verifying the cause of death in great aunts and great uncles they are excluded from the continuing study report covering 1979–1986 (table 2). The cause of death for parents' siblings, half siblings, nieces, and nephews was usually verified by the grandparents who were often present at the interviews, or were contacted by telephone. If there was any doubt, necropsy reports were studied.

Data collected in 1979 indicated differences in the obstetric histories of the mothers of infants who died of SIDS and who had a family history of SIDS, compared with those without such a history.[3] This led to a search for differences between families which had had two infant siblings that died from SIDS and families in which a single infant died from SIDS.

ESTABLISHING CAUSE OF DEATH OF INFANTS DYING IN SOUTH AUSTRALIA, 1965–1986

A list was made from records held at the office of the Registrar of Births, Deaths, and Marriages in Adelaide of the names of all children between the ages of 2 weeks and 2 years who died in South Australia between January 1965 and December 1985. This began in 1970 and was retrospective from 1965 to 1969, but recorded from notification from 1970.

The causes of death were ascertained by studying necropsy reports as the Adelaide Children's Hospital. This uncovered 70% of all infant deaths in South Australia and 84% of sudden unexpected infant deaths. For those children who did not have a necropsy at the hospital a search of hospital records was made and if these mentioned potentially fatal disorders these were recorded. From this source we discovered a further 7%. For the remainder the death certificate at the Registrar of Births, Deaths, and Marriages was examined. If the cause of death

Table 2 *Incidence of previous SIDS in first, second, and third degree relatives of infants who died from SIDS*

Relatives (degree)		*Years*	*Total No*	*No who died from SIDS*	*No of SIDS/1000 live births*	*95% Confidence intervals*
First—	Siblings	1973–86	660	14	21·2	9·5 to 33·0
Second—	Half siblings	1973–86	43	1	23·3	
	Maternal aunts and uncles	1979–86	673	10	14·9	
	Paternal aunts and uncles	1979–86	630	3	4·8	
	Total second degree		1346	14	10·4	4·6 to 16·2
Third—	Mothers' half siblings	1979–86	20	1	50·0	
	Fathers' half siblings	1979–86	23	1	43·5	
	Maternal first cousins	1979–86	639	6	9·4	
	Paternal first cousins	1979–86	628	2	3·2	
	Total third degree		1310	10	7·6	2·5 to 12·7
Total			3316	38	11·5	5·2 to 12·8

Significant difference (p<0·0001) for first degree, second degree, and third degree relatives when compared with overall incidence of SIDS in South Australia (2·1 per 1000) using two tailed z test [8] was clear (for example, drowning) this was recorded, resulting in a further 20%. For the remaining 3% in which the cause of death was not completely clear from the death certificate (for example, asphyxia) further information was obtained by either contacting the medical practitioner who signed the death certificate or studying the necropsy reports at the office of the Attorney General's Department, or contacting the hospital where the infant died.

OBTAINING CLINICAL, FAMILY, AND OBSTETRIC HISTORIES

Since 1973 the families of most of the infants who died suddenly and unexpectedly (99% of those in Adelaide, 80% in the whole of South Australia) have been interviewed by one or both of the authors, the first interview usually occurring within 24 hours of the infant being found dead or moribund. Data were recorded on a form. Several questions have been included since 1973; others have been added at varying times. Those relating to this paper include questions about parity and previous infant death (from 1973), previous miscarriage (from 1976); bleeding during pregnancy (from 1978); full family history, including total numbers of first to fifth degree relatives and all stillbirths, infant, child, and young adult deaths in first to fifth degree relatives (from 1979); and social grade. From 1977 families were given a rating from 1–5 by the author after visiting the home. This was done subjectively by noting several factors including the type of house, the area in which they lived, the condition of the house and grounds, the education of both parents, and the present employment of the parents.

Data were obtained for families not interviewed from examination of birth certificates, contacting local doctors, and contacting hospitals where the infants were born.

OBSTETRIC HISTORY CONTROL SERIES

Questionnaires were sent to the mothers of 200 infants whose births were consecutively registered on two days in March 1984, three months after the birth was registered. Twelve were returned unknown at that address, for nine the infant was over 4 months of age when the reply was received, 20 did not reply. For seven infants the answers about obstetric history were not accurate enough for inclusion. One hundred and fifty two replies are included, which represents 81% of those mothers believed to have received the questionnaire.

Results

Between January 1970 and December 1985, 1726 infants in South Australia died between 2 weeks and 2 years of age. Six hundred and forty eight were classified as SIDS, an overall rate of 2·0/1000 live births. If the 15 infants who died from SIDS in the first two weeks of life, and the four 2 year old infants who died from undetermined causes in the same time span are included, the incidence of SIDS is 2·1/1000 live births.

INCIDENCE OF SIDS IN FAMILIES

The infant mortality among previous siblings in first, second, and third degree relatives of 60 children who died of SIDS and a control group of 53 children is shown in table 1. First degree relatives are siblings and parents; second degree relatives are half siblings, aunts, uncles, and grandparents; and third degree relatives are the parents's half siblings, cousins, great aunts, great uncles, and great grandparents. The incidence of SIDS in the families of infants who died of SIDS was much greater than in control families. The infant mortality from conditions other than SIDS was similar in the two groups.

Table 2 shows the incidence of SIDS among previous siblings in first, second, and third degree relatives. The previous incidence of SIDS among siblings, aunts, uncles, and cousins was ascertained from retrospective recall when the parents were interviewed. For siblings and half siblings data were collected from January 1973. For 213 families in which one or more infants died between January 1979 and July 1986 full family histories including data about all second and third degree relatives were collected.

Between January 1973 and July 1986 545 infants died from SIDS. At the time of their death these infants had a total of 660 full siblings who were born alive. One infant had a twin sibling who died from SIDS in the same night. Thirteen other infants had a sibling (one infant, two siblings) who had previously died from SIDS (12 in South Australia, two in other states). Excluding the twin pair this is an incidence of 21·2/1000 siblings, or 10·1 times the expected rate. At the time of death the 545 infants who had died of SIDS had 43 half siblings, one of these had died from SIDS. The incidence among the full siblings of the parents was 13 in 1303 or 10·0/1000. This is 4·7 times the expected risk. The incidence among the parents' half siblings, nieces, and nephews was 10 in 1310 or 7·6/1000 (3·6 times the expected risk). The incidence was higher among the mothers' relatives (12·8/1000) than among the fathers' relatives (4·7/1000).

Table 3 shows the incidence in the mothers' next child. Between January 1970 and September 1986 690 infants under 3 years of age died from SIDS. Twelve families had two full siblings die from SIDS (including one pair of twins) and one mother had

Table 3 *Histories of families with two or more infants who died from SIDS between 1970 and 1976*

Family No	*History*	*Age at death (months)*			*Next child*
		First child	*Second child*	*Third child*	
1	Twin boys (died); two single boys (survived)	5	5	NA	1
2	Two miscarriages, one boy (died), one girl (died)	3	0	NA	1
3	Two boys (died), one girl and four boys (survived)	14	4	NA	1
4	One girl (died), one boy (died)	24	8	NA	1
5	One boy (died), one boy (survived), one boy (died)	2	3	NA	0
6	Four miscarriages, one girl (died), one miscarriage, one boy (survived), one miscarriage, one boy (died)	4	7	NA	0
7	Three miscarriages, one stillbirth, one girl (died), one neonatal death, one boy (survived), one boy (died)	17	12	NA	0
8	One miscarriage, one girl (survived), two boys (died)	6	0	NA	1
9	Two miscarriages, one girl (survived), two boys (died), one boy (survived)	2	4	NA	1
10	One girl (survived), two boys (died), one boy (survived)	1	8	NA	1
11	One girl (survived), one girl (died), one boy (survived), one boy (died)	2	1	NA	0
12	One miscarriage, one girl (survived), one boy (died), one girl (survived), one girl (died)	2	1	NA	0
13	One miscarriage, one boy (survived), one girl (survived), one miscarriage, one girl (died), one boy (died)	1	2	NA	0
14	Two boys (died); one girl (died)	2	19	1	2

Families 4 and 14—parity not gravidity known, family 8—half siblings (same mother) NA=not applicable

two infants who died from SIDS who had different fathers. Two families had had a previous infant die from SIDS (including one of the families with two SIDS deaths between 1970 and 1986). One family had had an adopted infant who died from SIDS before 1970 Excluding the twin pair, for nine SIDS infants it was the next born sibling who died from SIDS (table 3). Of the 654 families in which one or more infants died from SIDS between 1970 and 1985, 17 mothers are known not to have had further children. The maximum number of next born siblings is therefore 637. Of these, seven infants are known to have died from SIDS Therefore the minimum incidence in next born siblings is 11·0/1000, or 5·2 times the general population risk. The exact incidence in next subsequent siblings cannot be given, as some families who have moved from South Australia may have had another infant who died of SIDS and the exact number of subsequent siblings is not known. In South Australia the incidence of SIDS among twins is double the incidence among singletons. The increased risk is significant for twins weighing less than 2000 g at birth (4·4 times the expected risk) but not for twins weighing over 2000 g at birth (78% of twins) Between 1970 and 1986 three infants who died from SIDS had had a twin die previously (one early intrauterine, one late intrauterine, and one intrapartum death) One pair of twins both died during the same night Twenty three twins were found dead while their twin was alive Five surviving twins have used home apnoea alarms. No surviving twin of a SIDS victim has subsequently died. One triplet has died from SIDS, the other two remain alive and well.

The number of infants adopted in South Australia has fallen steadily since 1970, and in the year July 1970 to June 1971, 635 infants under 1 year of age were adopted. By the year July 1973 to June 1974 this had fallen to 266. In the four year period July 1970 to June 1974 a total of 1704 infants under 1 year of age were adopted. Of these, four infants died from SIDS (2·3/1000). In 1971 a twin boy aged 3 months died from SIDS. As well as his twin he had two natural siblings. An adopted sibling aged 1 month had died from SIDS six years earlier.

SIDS IN SIBLINGS

Table 4 shows the ages of siblings who died from SIDS were more variable than the ages of SIDS victims without SIDS in a sibling, one fifth of siblings who died from SIDS being over 12 months of age. Thirty six infants over 12 months of age died from SIDS between 1970 and 1985. Two of these were siblings. Of the 35 families who had an infant over 12 months of age with SIDS, four had a recurrence in a sibling (11%). Of 676 first SIDS in a family 641 (95%) were under 12 months of age. The recurrence in families who had a child die from SIDS in this age range was eight in 641 families (1%).

There were also unexpected, unexplained deaths in children and young adults. In the family with three infants who died from SIDS, the father's

Table 4 *Age at which infants died of SIDS in South Australia, January 1970–September 1986*

Age at death	*Single deaths from SIDS (n=662)* No (%)		*Deaths from SIDS among siblings (n=25)* No (%)	
<7 days	4 (0·6)	40 (6)	0	
7–14 days	11 (2)		1 (4)	2 (8)
14–30 days	25 (4)		1 (4)	
1–6 months	505 (76)		14 (56)	
6–12 months	86 (13)		4 (16)	
12–24 months	28 (4)	31 (5)	4 (16)	5 (20)
24–30 months	3 (0·5)		1 (4)	

These figures exclude twins who died at 5 months, two siblings who died elsewhere at 2 and 4 months, respectively and one infant whose adopted sibling died before 1970

mother died suddenly at 29 years and no cause for death was found at necropsy. In a family who moved to South Australia after two infants had died from SIDS in New South Wales, the father died at the age of 28 while he was sitting with friends after a game of squash. He showed no signs of distress before his sudden death for which no cause could be found at necropsy. His sister at 24 years of age collapsed while dressing to go out she was ventilated by bag and mask in the ambulance and given artificial ventilation in hospital, but she never regained consciousness and died. She had had asthma in the past and at necropsy hypoxic brain damage was found, thought to be secondary to asthma. The cousin of another family in which two siblings had died from SIDS was running across the lawn at the age of 2 when she collapsed and died. Heart failure was diagnosed, although until the time of her death she had seemed completely healthy.

During the past eight years details of all deaths of children and young adults have been obtained from the 274 families interviewed whose infants have died from SIDS Only one family with a single infant dying from SIDS has described such an unexpected unexplained death.

Table 5 shows the incidence of SIDS according to the mothers' obstetric histories. Though history of previous miscarriage was recorded from 1976, a history of bleeding in the first three months of pregnancy has only been sought since 1978. In the last 206 families with one infant dying from SIDS the incidence of previous miscarriage and bleeding in the first three months of pregnancy was no higher than in the mothers of a cohort of 152 successively registered singleton infant births.

In 12 families in which a sibling died of SIDS (including one family with SIDS before 1970) eight mothers had had at least one miscarriage before the first death from SIDS (table 3) One of these had two further miscarriages between the two infants who died from SIDS, and one a neonatal death of an extremely premature infant between the two deaths from SIDS. Details were obtained about bleeding in pregnancy for 16 of those in which a sibling had died of SIDS; eight pregnancies had been complicated by vaginal bleeding during the first three months. One further pregnancy was complicated by bleeding at four months' gestation. In the remaining seven pregnancies there was no bleeding Previous stillbirth of a normally formed infant occurred in one of 12 families in which two siblings had died from SIDS and five of 413 families in which one infant had died from SIDS.

Some unusual pathological findings were recorded. In reviewing the histological reports of some of the siblings who had died of SIDS, Professor J Emery (personal communication) noted bronchomalacia in both boys in one family. He did not feel that this was sufficient explanation for death, but had never observed this before in many hundreds of infants with SIDS. Interestingly, one of the brothers who died from SIDS at 3 months of age was noted to have an odd cry, described by the parents as 'like a bleating sheep' His sibling who died at 2 months of age had had a pyloroplasty at 14 days of age. Recovery from anaesthetic took longer than expected but he was otherwise well. At 5 weeks of age he had an episode of loud gasping

Table 5 *Comparison of obstetric complications among the groups*

	Previous miscarriage			*Vaginal bleeding during first three months of pregnancy*		
	No	*%*	*95% Confidence intervals*	*No*	*%*	*95% Confidence intervals*
Control group (n=152)	36	23·7	16·6 to 30·8	23	15·1	9·1 to 21·2
Mothers with a single death from SIDS (n=206)	39	18·9	13·3 to 24·5	21	10·2	5·8 to 14·6
Mothers with more than one death from SIDS (n=12 for miscarriage and 16 for vaginal bleeding)	8	66·7*	34·3 to 99·1	8	50·0*	14·0 to 86·0

*Significant difference ($p<0.005$) when compared with mothers with a single death from SIDS, using χ^2 test with one degree of freedom[8] followed by shallow breathing, which lasted for about 10 minutes during which he was cold and clammy all over. The father of the two boys had chest pain and cough with every upper respiratory infection and required admission to hospital with pneumonia when 26 years old The paternal grandfather often had episodes of gasping for air as a young adult and became extremely breathless with upper respiratory infections He caught a 'cold' at 62 years, began gasping for breath, was admitted to hospital but died four days later from upper respiratory infection. The paternal grandmother's brother (third degree relative) had been found dead in his cot, having been thought well, at 7 weeks of age. In another family who now have five living children, the first was admitted to hospital at 14 months of age having swallowed cleaning fluid. He developed mild pneumonitis, was well following discharge from hospital, but was found dead in his cot 10 days later At necropsy there were multiple foreign body granulomata in the lungs, although the lungs were well aerated. The second child in the family was found dead in his cot at 4 months of age; there were no unusual histological findings.

The homes of 445 infants who died from SIDS have been visited by one of us in the past 13 years; 14 families lived in severely deprived conditions. Two of these families have had a further death from SIDS, one of them being the most severely deprived of all homes visited.

None of the families with recurrence in a sibling in this series had a history of SIDS in a second degree relative. There was one in which SIDS occurred in a third degree relative, and one in a fifth degree relative. Of the 213 families studied in detail, one mother had two brothers who died from SIDS, and another infant's father's brother and the mother's half brother had died from SIDS. The first infant of this mother had one episode of pronounced apnoea requiring mouth to mouth resuscitation, the second infant died from SIDS, and the third infant (who required regular thyroid supplement for congenital hypothyroidism) had several attacks of apnoea while on a home alarm system.

Discussion

In Norway all live births are recorded in a Medical Birth Registry.[6] The official national person number system enables longitudinal follow up of all mothers to be carried out with respect to the results of their pregnancies. This is linked to the official system of death registration. Apart from families who may emigrate this enables accurate evaluation of recurrence of SIDS in subsequent siblings. It seems that in that series the recurrence is in the mother's next subsequent child, which includes half siblings on the mother's but not the father's side. Using this system and including deaths occurring between 7 and 364 days of age, SIDS in the next subsequent sibling (? mother's next child) in Norway was found to be 4·4 times the expected incidence Such a numbering system is not used in South Australia, so the exact number of next subsequent infants is not known. Most mothers in South Australia who have an infant who dies from SIDS have further children; 81% of married couples who had an infant that died from SIDS in 1980 are known to have had a subsequent child by January 1986, and 72% of mothers in Adelaide who had an infant that died from SIDS in 1985 had become pregnant by July 1986.

In the same age range as the Norwegian study (7 to 364 days) between 1970 and 1985, 603 of the families that we studied had their first infant die from SIDS in South Australia. Of these mothers eight have had a further death in the same age range, four in the next subsequent child. Extrapolating from the previous data that showed that 81% of families in which a child died from SIDS in 1980 had another child by 1986, it is thought that between 80% and 100% of such mothers have another child. This means that the incidence in the next subsequent child in the 7 to 364 days age group may be estimated as being between 4 in 693 and 4 in 482, or a rate of 6·7 to 8·3/1000 which is 3·5 to 4·4 times the rate expected in this age range (1·9/1000); this is similar to the relative risk in Norway. When infants dying at 12 to 24 months are included, between 1970 and 1985 a further 35 families had their first infant die from SIDS in South Australia. Of these four had a recurrence, three in the next subsequent infant, making a total of seven in the mother's next subsequent child in a maximum of 638, or a minimum rate of 11/1000, five times the expected rate of 2·1/1000 in this age range.

Peterson found mothers in families in which more than one infant had died from SIDS had considerably fewer full brothers and sisters and proportionately more half, step, or adopted siblings than their spouses and the mothers and fathers of all other SIDS probands.[5] In the families with more than one case of SIDS in this study one mother was adopted. Ten mothers had 41 siblings (including one neonatal death of a full sibling) and four half siblings Ten fathers had 32 siblings, one stillborn full sibling, two half siblings, and one step sibling (who died from SIDS).

Both genetic and environmental factors seem to contribute to recurrence of SIDS in families in South Australia, and indeed the gestation and environment of infant siblings tends to be similar. The environmental influence is illustrated by the occurrence of SIDS in two infants in one family, one being natural born and the other adopted; the only incidence of both twins dying being on the same night; and the recurrence in two severely socially deprived families. The genetic influence is shown in the three families with deaths in young adults or children and the family in which two infants had bronchomalacia.

In 1980 in South Australia the average family size was 2·4 children. Assuming SIDS to be a sporadic event this means an incidence of SIDS of about one in every 200 families. Between January 1970 and September 1986, 677 families in South Australia had an infant who did from SIDS; for 13 families it was a recurrence of SIDS This is an incidence of one in 52 families, or about four times the expected risk.

Six hundred and twenty six of the 677 families (92%) had their first infant death from SIDS between 2 weeks and 12 months of age, were not severely socially deprived, had no family history of sudden unexpected unexplained deaths in children or young adults, and no bronchomalacia at necropsy Five of these familes have had a subsequent infant die from SIDS (an incidence of one in 126 families, or 1·6 times that expected), three of these being the next subsequent child (0·5% incidence in next child). It seems reasonable to reassure these families that it is unlikely to happen again.

The risk for a few families (less than 10% of SIDS) is significantly increased The only family with bronchomalacia found at necropsy, three out of four families with a history of sudden unexpected unexplained deaths in children or young adults, four of 35 families in whom the infant who died from SIDS was over 12 months of age at the time of death, and two of the 14 families who were felt to be severely socially deprived, had a recurrence in a sibling. Although numbers in this study are too small to give exact risks, in families with any of these factors, particularly if the mother has a history of miscarriage or bleeding during the pregnancy, the subsequent child should be considered 'at risk'.

Recurrence in families relates to the incidence in a community or race. Where the incidence is low—for example in Sweden or Asia—recurrence is extremely rare. It also relates to the size of the family; the more infants born into a family the more likely is it that there will be a recurrence. There are many reasons for large families (cultural and religious) but good counselling at the time of the death from SIDS and the increased appreciation by parents of the importance of children and families, are likely to explain part of the difference in reported family recurrences in different communities

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Combined familial adenosine deaminase and purine nucleoside phosphorylase deficiencies

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SUMMARY We studied an Arab family in which two infants died of severe combined immunodeficiency caused by adenosine deaminase (ADA) deficiency. One infant had purine nucleoside phosphorylase (PNP) activity in the leucocytes only half that of normal. Four other infant siblings had previously died from infections before the age of 2 months. Hyperpigmented skin lesions preceded death in three cases. The healthy parents and three healthy siblings aged 4–9 years had varying degrees of both ADA and PNP deficiencies in both white and red cells. ADA deficiency was pronounced in two siblings, and mild in the third and in the parents, and PNP activity was severely deficient in one sibling, and moderately deficient in the parents and other two siblings, who were all well. Complete absence of ADA from white cells lead to the development of severe combined immunodeficiency, but even minimal residual ADA and PNP activity allowed maturation of the immune system with normal immune function.

Severe primary or hereditary combined B cell and T cell immune deficiency is rare, and unless treated with bone marrow transfusion (or fetal liver transplantation) is universally and rapidly fatal. Milder degrees of combined immune deficiency have been described in various syndromes, including Nezelof's syndrome, ataxia telangiectasia, chronic mucocutaneous candidiasis, short limbed dwarfism, Letterer-Siwe disease, Wiskott-Aldrich syndrome, and DiGeorge's syndrome. In most of these conditions the defect leading to the immune deficiency is unknown. A group of patients with severe combined immunodeficiency has, however, been described who have a congenital deficiency of certain enzymes that are part of the purine metabolic cycle. Deficiency of adenosine deaminase (ADA) has been found in at least 20% of cases of the autosomal recessive type of severe combined immunodeficiency, and deficiency of purine nucleoside phosphorylase (PNP) is associated with a selective cellular immune deficiency.

We report an Arab family in which four infants died within two months of birth from severe infections, particularly pneumonia and diarrhoea, which in retrospect could have been due to severe immune deficiency. Two infants who had been born recently and who had recurrent infections were studied and found to have severe combined immunodeficiency with ADA deficiency, while varying degrees of both ADA and PNP deficiencies were found in other healthy members of the family (figure).

Case reports

CASE 1

A healthy male infant weighing 3000 g was born to healthy, unrelated parents. Three siblings, two boys and one girl aged 4–9 years, were alive and well, and

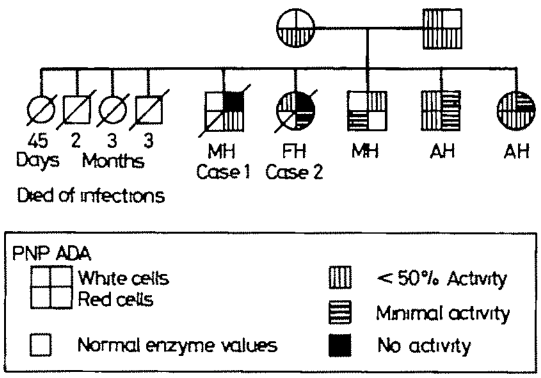

Figure *Pedigree of Arab family with combined ADA and PNP deficiencies* four others had died within two months of birth of severe diarrhoea or pneumonia. The proband was examined at 7 days of age when there were no abnormal findings. Within a few weeks he developed a cough, and became cyanosed when feeding or crying. At the age of 1 month the parents noted hyperpigmented macules about 1 cm in diameter on the skin of his legs, groin, and arms. They had noticed similar spots on two other infants before their deaths, and so the infant was taken to the local doctor. The child did not appear to be particularly ill, had no fever or diarrhoea, although he did have mild cough. His weight was only 3200 g and there were a few rales at the bases of both lungs. After preliminary laboratory studies the baby (aged 6 weeks) was referred to the Kaplan Hospital with a diagnosis of possible severe combined immunodeficiency.

He weighed 4000 g, and apart from a mild respiratory tract infection appeared comparatively well. There were several pigmented spots on his skin, and according to the parents these had become larger and more pronounced since birth. Histological examination of a biopsy specimen taken from one of the spots was not helpful. His haemoglobin concentration was 150 g/l white cell count 6–9×10⁹/l, and lymphocytes 0·18–0·90×10⁹/l. Liver function studies and concentrations of proteins, electrolytes, urea, creatinine, and complement were all within normal limits An electrocardiogram was normal. Serial *x* ray pictures of the chest showed progressive bilateral bronchopneumonia, which did not respond to treatment with antibiotics. No thymic shadow was seen on lateral *x* ray pictures of the mediastinum. *X* ray pictures of the skeletal system showed flaring of the costochondral junctions, and changes at the vertebrocostal junctions similar to those found in cases of ADA deficiency.[1 2] Examination of the bone marrow showed severe lymphopenia. Table 1 gives a summary of the immunological studies. There was severe T cell deficiency (on one occasion there were 2% T rosettes, and on another 6%) and a developing B cell deficiency. Delayed hypersensitivity skin tests were negative. Severe combined immunodeficiency seemed the most likely diagnosis, so it was decided to treat the infant by bone marrow transplantation. He suddenly developed severe respiratory distress, however, and died within a few weeks with bilateral pneumonia, severe diarrhoea, liver dysfunction, and renal failure. At necropsy generalised jaundice, patent liver ducts, and regional consolidation of both lungs were found; there was a rudimentary, minute thymus with some Hassall's corpuscles on histological section and small, shotty lymph nodes with diminished T zones.

Before death blood had been taken for specific lymphocyte enzyme studies but the results were only received later. When it become known that the infant indeed had deficiency of ADA in the white cells with low activity in the red cells, estimations of ADA and PNP activity were performed on the rest of the immediate family (table 2) using the technique of Beutler for ADA,[3] and that of Kalckar for PNP.[4]

CASE 2

A sister of case 1, was referred at 13 days of age for immunological studies because of her family history. She weighed 3850 g, did not appear to be ill, behaved normally and sucked well. No abnormali-

Table 1 *Results of immunological studies—Case 1; normal values are given in parentheses*

Test	*Result*
Total lymphocyte count (×10⁹/l)	0·18–0·9 (>1·5)
T cells (rosettes)	2–6% (70%)
OKT3 (fluorescence activated cell sorting)	1, 28% (70%=>1·2)
OKT4 (helper cells)	1, 18% (50%=>0·75)
OKT8 (suppressor cells)	1, 17% (30%=>0·45)
B cells (surface membrane immunoglobulin)	10% (10–20%)
Proliferative response of mononuclear cells.	
To phytohaemagglutinin	Absent
To concanavalin A	Absent
Delayed hypersensitivity skin tests to phytohaemagglutinin, mumps, and Candida	Negative
Examination of bone marrow aspirate	Severe lymphopenia
Immunoglobulin concentrations at 6, 8, and 10 weeks of age (g/l)	
IgG	3·5, 4, 3
IgA	<0·2, <0·04, <0·04
IgM	0·6, 0·95, <0·12
IgE (at 8 weeks only)	<0·03
Interferon production during infections	53 U/ml (normal)
White cell chemotaxis	Normal
Nitroblue tetrazolium test	Normal
Phagocytosis	Normal

Table 2 *Estimations of ADA and PNP activity in the blood of the members of the family being studied*

	Red cells (mM/second/g haemoglobin)		*White cells (mM/hour/10⁸ cells)*	
	ADA	*PNP*	*ADA*	*PNP*
Mother	0·4, 1·4	10	0, 3·0	26
Father	0·18	7·7	4·6	28
Son ([illegible]H)	0·57	3·9	1·97	44
Son (AH)	0·05	11	0·09	8
Daughter (AH)	0·17	9·4	0·54	8
Case 1 (MH)	0·2	25	0	42
Case 2 (FH)	0·2, 0	25, 17	0, 0	12, 13
Normal ranges	0·7–1·0	20–30	1·5–9	8–28

ties were found on physical examination and there were no pigmented spots. Her haemoglobin concentration was 130 g/l, white cell count $3{\cdot}2\times10^9$/l, and the lymphocyte count was only $0{\cdot}45\times10^9$/l. Immunoglobulin concentrations were within normal limits but T cell rosettes were not found. An *x* ray picture of the chest showed mild lung opacities and a narrow mediastinum. ADA was absent from the patient's white cells and there was only low activity in the red cells. White cell PNP activity was about 50% of normal (table 2). Repeat investigations showed similar results, except that on this occasion ADA activity was also absent from the erythrocytes. HLA typing of the family was performed and one of the brothers was found to be a suitable bone marrow donor, although the ADA and PNP activities were low in both red and white cells. Arrangements were made for urgent bone marrow transplantation but the family withdrew consent and the infant died of bronchopneumonia.

Discussion

ADA and PNP are both enzymes that catalyse reactions in the purine catabolic pathway. ADA catalyses the conversion of adenosine to inosine, and PNP catalyses the conversion of inosine to hypoxanthine and of guanosine to guanine. Deficiency of ADA results in the accumulation of deoxyadenosine triphosphate in red and white cells, while in PNP deficiency there are raised concentrations of inosine, guanosine, deoxyinosine, and deoxyguanosine in the blood and increased secretion of their metabolites in the urine. Increased amounts of these metabolites are toxic to cells, with deoxyadenosine triphosphate being somewhat more toxic to lymphocytes than deoxyguanosine triphosphate. The latter has a specific toxic effect on T cells rather than B cells, and therefore the immune deficiency is usually more extensive if ADA is deficient.[5] The nature of the defect in ADA deficiency is still not clear, though it has been suggested that there might be a mutation in the gene for ADA leading to total deficiency and severe combined immunodeficiency,[6 7] and genetic heterogeneity leading to partial deficiency.[8] In PNP deficiency the genetic defect is almost certainly in the PNP gene locus itself, which is situated on the long arm of chromosome 14 [7].

The correlation between ADA deficiency and immunodeficiency was first suggested in 1972 by Giblett *et al*[6] and three years later confirmed by Meuwissen *et al*.[1] It has subsequently been shown that ADA deficiency is present in at least 20% of cases of the autosomal recessive type of severe combined immunodeficiency.[7] Several reports have appeared, however, indicating that deficiency of ADA can occur without immunodeficiency,[9–12] though it now seems that in most cases of ADA deficiency with no immune deficiency some minimal residual ADA activity is present in the cells. Jenkins *et al* described a healthy !Kung boy (a member of a black Bushman tribe in southern Africa) who had almost negligible amounts of ADA in both cells types.[7 9 10]

Only about 20 patients with PNP deficiency have been described (Stoop JW, Zegers BJM, personal communication). Symptoms of immune deficiency may appear later in life; patients have been described who had normal immune function at birth, immunological deterioration occurring by the age of 2–3 years The clinical picture suggests severely impaired T lymphocyte function, whereas B lymphocyte function is at least in part intact. No bone abnormalities have been found on radiography, but neurological abnormalities have been described.[7 13]

The first case in this family that we studied had no ADA activity in his white cells and diminished activity in his red cells, and the clinical picture and course were typical of severe combined immunodeficiency The T cell deficiency was extreme, and the B cell deficiency became apparent at the age of 10 weeks. The high concentrations of IgM in the first two blood samples were unexpected and may have been caused by normal IgM production antenatally when theoretically ADA could have been supplied by the mother. In the samples of blood taken at 10 weeks of age IgM was not detected. Because the results of the enzyme studies were received after the baby's death, no efforts could be made to attempt temporary replacement treatment with irradiated red blood cells

Severe combined immunodeficiency with ADA deficiency was diagnosed early in the second patient who could have benefited from bone marrow transplantation from her histocompatible brother, but further treatment was refused

The results of the enzyme studies performed on the patient's family were remarkable in many respects (table 2). The father had low values of ADA and PNP in his red cells, but normal values in his white cells. At the time of writing he is leading a normal life with no evidence of immune deficiency. The mother, also well, had enzyme assays on two occasions; on the first, ADA values in her red cells were low and there was no activity in her white cells, and on the other occasion ADA activity was within normal limits. PNP activity in her red cells was low. These discrepancies are hard to explain and somewhat disturbing The possibility of variations in technique because the repeat assays were done (albeit with normal controls) on different occasions were considered, as was the contamination of white cells by red cells during the assay. The latter is unlikely because of the normal ADA values in both cell lines and minimal or even moderate contamination of cells could not have caused this increase on the second occasion. In addition, repeat assays done simultaneously on the mother and proband 2 showed good reproducibility. The son AH had extremely low ADA activity and moderately decreased PNP values in both red and white cells. The daughter AH also had low ADA and PNP values in both cell types. The son MH had low ADA activities, as well as extremely low PNP activity in his red cells. Like their parents, these three children lead normal, healthy lives and did not seem at the time of writing to have any defects of their immune systems. Cases 1 and 2 had severe ADA deficiency in both cell lines with normal PNP values.

It is difficult to explain the partial deficiency of two enzymes which, as far as we know, are unrelated except that they both play part in the purine metabolic cycle. It could be that there is some primary deficiency at some other point in this pathway, or a deficiency of a control protein for both enzymes. We can find no evidence for either hypothesis It may be that the deficiency of one is secondary to the deficiency of the other. This is not likely, as in some family members PNP activity was normal despite deficient ADA activity, and in others both were deficient.

As far as we know no case report of combined ADA and PNP deficiency has been published. It seems from our study that even minimal residual amounts of ADA and PNP in white cells are sufficient to allow maturation and development of immune competence in some or all white cells None of the subjects studied had complete PNP deficiency, but two infants with total ADA deficiency in their white cells developed severe combined immunodeficiency and died. For social reasons further investigations of this family has not been possible.

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Teenage relationships and sex education

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SUMMARY Most of the consequences of early intercourse affect the woman and much research has focused upon her. As part of a study on teenage pregnancy, where 137 women were interviewed, 46 men were also interviewed. They were less likely to have had teaching about sex from parents and were subject to less parental supervision than the women. Both sexes had had similar experience of school sex education. Just under half of the men started having intercourse before 16 years. Over half of both sexes were initiated by an experienced partner and for 15/25 (60%) of the men this was within the first month of a relationship. Most men had had several partners and 27/99 (27%) of teenage women at least three, most in the context of stable relationships. 'Serial monogamy' exposes each partner indirectly to their partners previous partners (with the associated medical risks). Education must help teenagers make decisions about sexual involvement that take account of these facts and the implications for their own future health and happiness.

Early teenage intercourse and pregnancy are associated with medical, economic, social, and psychological problems. The woman experiences most of the consequences of sexual activity and possibly because of this and difficulty of interviewing male partners, research has tended to focus upon her. Over the last 20 years there have been three reported surveys in the United Kingdom concerned with teenagers' attitudes to sex and sex education.[1–3] These studies have sampled the general teenage population and have not considered the selective population of men whose sexual activities may have led to a teenage pregnancy. If sex education in its widest sense is to be appropriate, the attitudes of both men and women to relationships and teaching need to be evaluated.

A study of teenage pregnancy undertaken in a health district containing a small city that has a stable indigenous and semirural population had recently been published.[4] This provided data that were unbiased by important religious or ethnic differences. One hundred and one women pregnant before their 18th birthday were interviewed to provide information about their family background, their relationships with the opposite sex, and the knowledge that they had gained from sex education. Thirty six primigravidae aged between 20 and 25 years were also interviewed as a comparison population of young women who had not become pregnant in their teens.

Towards the end of that study, 46 men were also interviewed: 16 were partners of pregnant teenagers (the 'study' group) and 30 were partners of the primigravidae aged between 20 and 25 years (the 'comparison' group).

The behavioural and educational aspects of the data collected from both the groups of men and women in the study were of particular interest. Despite the small sample size, we hoped to be able to identify important areas of concern for current sex education programmes and to provide information for those concerned in the care of teenagers. This paper reports the data from the men and comparisons of men and women with particular reference to educational aspects.

Subjects and methods

The men were recruited to the study by their partners, who were in hospital after either delivery or a termination. Initially, many of the men were reluctant to be interviewed because of embarrassment and concern about confidentiality, but only one refused to participate. The men whose girlfriends were under 18 years and pregnant were difficult to find for various reasons. Many girls were no longer in contact with their boyfriends and, where they were having a termination, their boyfriends often did not visit for the 48 hours that they were in hospital Sampling of the men was therefore biased by their availability.

All interviews were carried out in private by a male doctor (WLC), in hospital, using a similar questionnaire to that which had been used for the women. The questionnaire provided both codified information and data from general comments and discussion. The detailed questions were concerned with family background, school background, degree of parental supervision, sex education received from home, school, and friends, personal relationships, factors surrounding first intercourse, and the pregnancy itself Four discussion areas concentrated on how the young man thought sex education in school could be improved, future expectations, the information he wished he had received, and the advice he would give to a younger sibling or friend.

Ethical committee approval was given for the studies on both men and women. The χ^2 test was used to test differences between the groups.

Results

FAMILY INFLUENCE ON RELATIONSHIPS AND EDUCATION

The men were much less likely to have had teaching from their parents than the women (table 1); there were no differences between the study and comparison groups. In particular, only a 10th of the men could remember discussing the general topic of relationships and under a fifth, contraception. The women were also subject to a much greater degree of parental supervision and constraint than the men (table 2). Twenty six (59%) of the young men did tell their parents where they were going, but only a quarter had to ask if they could go out, and only a third had a specific time by which to be home. Just under a third of the parents stayed up or stayed awake until their sons had returned, in contrast with three quarters of the parents of the women.

Table 2 *Extent of parental supervision*

Area of supervision	*Men (n=44)*	*Women (n=136)*
No (%) who needed permission to go out	10 (23)	98 (72)*
No (%) given a time to be home by	16 (36)	106 (78)*
No (%) whose parents knew where the young person was going	26 (59)	120 (88)*
No (%) given a limit to the number of times allowed out each week	6 (14)	39 (29)*
No (%) whose parents stayed up or awake until they returned home	13 (30)	97 (71)*

*Significant difference between the sexes, $p<0{\cdot}05$
n=Number with data for this question

SCHOOL SEX EDUCATION

Both the men and women had very similar experience of sex education in school. The nature and content of this education varied considerably from school to school—for example, in one a single sex education lesson was given to a whole year group, while in another sex education was part of a course run over several years. Most schools covered the basic biological facts about puberty and reproduction and almost half of the men and over half of the women remembered receiving some teaching on contraception and sexually transmitted diseases. Only a third of both sexes could recall any teaching about relationships and only a quarter of women and 5% of the men remembered any teaching about the subject of parenthood (commonly part of the curriculum for less academic girls).

Table 1 *No (%) of men and women who had received sex education within the family on various topics*

	Men (n=46)	*Women (n=137)*
Puberty/periods	7 (15)	99 (72)*
Relationships	5 (11)	53 (39)*
Contraception	8 (17)	56 (41)*
Sexually transmitted diseases	3 (6)	15 (11)

*Significant difference between the sexes, $p<0{\cdot}01$
n=Number with data for this question

Sex education was taught in a wide variety of subject lessons including biology, physical education, religious knowledge, separate sex education, child care and PSM (personal, social, moral). Some of the young people reported that teachers found it very difficult to give the lessons, and a few reported teachers as having to leave the class room because of embarrassment.

The young people gave various suggestions as to the way they thought sex education in schools could be improved· small discussion groups, the teaching to be started earlier, and for other professionals to come in from outside school to give lessons on specialist topics. Several felt that it would be easier to ask questions of professionals rather than teachers because of teachers' embarrassment and concern about confidentiality.

INFLUENCE OF FRIENDS

Twenty two (49%) of the men said they had learnt most about contraception, not from parents or schools, but from friends (table 3). This contrasted with the women who learnt most from parents and school. Women learnt most about relationships from discussion with friends, as did a third of the men however, half the men said they had learnt most for themselves. These men could not focus upon one source as the most important influence

Table 3 *Sources of information (figures are No (%))*

	Topic					
	Contraception		*Relationships*		*Sexually transmitted diseases*	
	Men (n=45)	*Women (n=132)*	*Men (n=38)*	*Women (n=85)*	*Men (n=46)*	*Women (n=97)*
Parents	1 (2)	30 (23)	2 (5)	26 (30)	1 (2)	11 (11)
Friends	22 (49)	30 (23)	15 (39)	43 (51)	16 (35)	11 (11)
School	14 (31)	41 (31)	2 (5)	6 (7)	18 (39)	61 (63)
Books	5 (11)	19 (14)	—	—	8 (17)	8 (8)
Themselves	—	—	19 (50)	11 (13)	—	—

n=Number with data for this question.

and although they said they learnt about relationships for themselves, it is probable that this covered a variety of sources. Most information on sexually transmitted diseases was learnt from school, although, again, a third of the men gave friends as the important source.

A total of 58 out of 74 (78%) of the teenage women and 11 (85%) of the men in the study group had the impression that at least half their friends were sexually active. Data for the men were only available for 13 of the study group. Forty per cent of both sexes thought that if people at school had a boyfriend or girlfriend then most would be sexually experienced by 15 years.

In an open coded part of the questionnaire, the young people were asked what information they wished they had received or what information they felt was important to pass on to younger siblings or friends. A third of the teenage women wanted more information on relationships and pressures, and this was significantly more than in the study group of men ($p<0{\cdot}05$). More striking was that significantly more men (21/30, 70%) than women (4/36, 11%) in comparison group wanted information or would tell siblings about the importance of contraception ($p<0{\cdot}001$). In the study group the trend was similar although it did not reach significance (men, 9/16, 56%; women, 36/101, 36%).

RELATIONSHIPS

Just under half of the men interviewed said they started having intercourse at under 16 years of age (table 4); this was in strong contrast with the comparison group of women, where only seven (19%) had first intercourse before this age. Of those women pregnant under 18 years, 76 (76%) had intercourse before 16 years and 47 out of 72 (65%) of these wished they had waited until they were older. About one half of the men who started having intercourse under the age of 16 felt, in retrospect, that they had been too young and wished they had delayed.

As expected, the man tended to be older than his girlfriend. In four cases, the men did not know whether their partner was experienced or not, but overall, 25 out of 44 (57%) of the men were initiated by women with previous sexual experience. Of the 25 men who knew their girlfriends were already sexually experienced, the expected age relationship referred to did not hold true with 50% of the women being older. Of the women in the study group 37 out of 63 (59%) first had intercourse with an experienced boyfriend, and the age relationship held true, with only three men younger.

The length of the relationship before first intercourse was inversely related to the experience of the partner: A total of 15 (60%) of the men who had an experienced girlfriend had intercourse within the first month, whereas when both partners were virgins three quarters waited until they had been 'going out' for more than one month. Similarly, for women at first intercourse, where both partners were virgins, only four (17%) had been going out for less than three months before intercourse occurred and five (21%) less than six months. Where the boyfriends were experienced, 18 (49%) of the virgin women had intercourse within the first three months and eight (22%) within the month.

Neither the seniority of the partner, nor their own age appeared to effect the reason for first intercourse; nine out of 44 (20%) of the young men said

Table 4 *Age at first intercourse (figures are No (%))*

	Study group		*Comparison group*	
	Men (n=15)	*Women (n=100)*	*Men (n=29)*	*Women (n=36)*
< 16 years	7 (47)	76 (76)*	14 (48)	7 (19)*
≥ 16 years	8 (53)	24 (24)*	15 (52)	29 (81)*

*Significant difference between sexes, $p<0{\cdot}05$.
n=Number with data for this question.

it was planned, and the same number felt pressurised either by their girlfriend or by society. Most of the young men said first intercourse was unplanned and a significant minority (14%) said this was related to alcohol. A third of the teenage women had made a conscious decision to have intercourse, and just under a fifth gave pressure as the reason but, as with the men, first intercourse was unplanned in just under half of the cases.

In both the groups of men and women in the study group, those who first had intercourse under 16 years were less likely to have used any form of contraception on the first occasion or to have continued to use it (table 5). In the study group of men under a third had used contraception and only one continued to do so. Six (75%) of the men in the study group who were over 16 years at first intercourse used contraception on the first occasion, but only four of them continued to do so. Eighteen (62%) of the comparison group of men of all ages used contraceptives regularly. Women in the comparison group who started intercourse under 16 were significantly more likely than the men under 16 ($p<0{\cdot}05$) to have used contraception on the first occasion but were not significantly more likely to have continued to do so.

The discrepancy in age in the study of the men made comparison of the number of partners difficult. In table 6 the total number of partners is shown as the numerator and the number of years sexual activity as the denominator for each man. In the comparison group none of those who started having intercourse under 16 years had had less than four partners and most had had over 10. Of those who started intercourse over 16 years, three had had a monogomous relationship, but again most had had several partners. In the study group, two of those who started under 16 years had only had one partner but the rest had had several over a short period of time. Two of those who had intercourse over 16 years had had only one partner.

Looking at the total number of partners the women in the study group had, only one had had more than 10 partners. Of the 76 who started intercourse under 16 years, 40 (53%) had had one partner but 23 (30%) had had three or more. Excluding those who had been sexually active for more than two years similar numbers of the study group men (50%) and women (38%) had had more than one partner. In the study group the women who started to have intercourse under 16 years had more partners than those over 16 years, although

Table 5 *No (%) of subjects using contraception at first intercourse and subsequently*

	Men				*Women*			
	Study group		*Comparison group*		*Study group*		*Comparison group*	
	<16 (n=7)	*≥16 (n=8)*	*<16 (n=14)*	*≥16 (n=15)*	*<16 (n=76)*	*≥16 (n=24)*	*<16 (n=7)*	*≥16 (n=29)*
First occasion	2 (29)	6 (75)	7 (48)	11 (73)	35 (46)	15 (62)	6 (86)	24 (83)
Regularly	1 (14)	4 (50)	8 (57)	10 (67)	18 (24)	12 (50)	5 (71)	18 (62)

n=Number with data for this question

Table 6 *No of partners/No of years sexual activity in men of both groups*

	Study group (n=14)			*Comparison group (n=28)*			
Age at first intercourse							
<16	1/1	1/2	15/3	15/4	9/6	25/6	9/7
	1/4	6/4	4/5	12/7	4/8	20/8	10/10
	7/5			6/11	7/13	25/13	80/14
				100/14	40/15		
≥16	1/1	1/1	3/1	1/1	1/7	1/10	24/5
	4/1	6/1	2/2	4/6	5/6	6/8	6/8
	3/7			11/8	3/9	10/11	4/12
				3/13	20/14		

n=Number with data for this question

this did not reach significance. In the comparison group half of those who were 16 years or over at first intercourse had had a monogamous relationship but this was so for only one of the women who started intercourse before 16 years. Overall, 16 (44%) of the comparison group had three or more partners.

Twelve pregnant teenage women and their partners were interviewed and from this one could calculate the average number of partners each had had and, therefore, the number of partners each was indirectly exposed to. The men had an average of four partners and the women two, thus exposing both indirectly to a minimum of eight other people at 'first generation' contact level.

A total of 13 (13%) of the women in the study group had experienced a previous pregnancy, most by the same partner. Eight (17%) of the men had caused a pregnancy in a different partner.

Discussion

Considering that puberty begins later in males than in females it is perhaps surprising to find that just under half of the men interviewed had begun sexual activity under 16 years, whereas of the women in the comparison group only a fifth had done so. A similar discrepancy has been observed in earlier studies in this country, Schofield in the early 1960s showed that 20% of men and 12% of women between 15 and 19 years were experienced.[1] A decade later Farrell suggested that 55% of men and 46% of women between 16 and 19 years had experienced intercourse.[2] Examination of Farrell's data show that 12% of all the women and 31% of all the men said they had had first intercourse before 16 years. These figures, which are of the same order, but less than our own, suggest that the rates of teenage intercourse are increasing though pregnancy rates are approximately static except perhaps in the youngest groups.[5]

Studies carried out in the United States, where there is a greater problem of teenage pregnancy, have shown that teenagers tend to have intercourse earlier than in this country.[6] Finkel and Finkel in their study on 400 male high school students showed that the mean age for first intercourse was 14·5 years for whites, with black and hispanic males having intercourse at 11·6 years and 13·0 years respectively.[7] This study also showed that 53% were initiated by older women.

It is commoner in relationships for the man to be older than his girlfriend and this is true for most relationships in this study. In the men, however, half had been out with women who were sexually experienced and often also older. These men were likely to establish a relationship involving sexual intercourse earlier than those who were going out with women who were the same age or younger and not experienced. Within the average relationship—that is where the man is older—it is also apparent that women going out with sexually experienced men are likely to indulge in sexual intercourse earlier. These data confirm the hypothesis that sexually experienced young people are more likely to initiate subsequent boyfriends or girlfriends into sexual intercourse and indicate that many young men who have an experienced girlfriend begin to have sexual intercourse within the first month of the relationship. Previous studies have usually stated that sexual intercourse among teenagers is acceptable in the context of a stable relationship, although the definition of 'stable relationship' is not usually given. It seems unlikely that most people would regard such short relationships as we have described above as being stable.

Most of men had had several partners and half of the women more than one; this is of importance when considering the risk factors for cervical carcinoma and sexually transmitted diseases. Most were not promiscuous, but had had sex in the context of a relationship with a single person while the relationship lasted—that is, serial monogamy. Serial monogamy, however, exposes each partner indirectly to previous partners and even counting the first generation contacts the number of exposures is large. Cervical carcinoma is known to be associated with age at first intercourse and number of partners,[8] and the incidence of this disease is increasing and presenting at a younger age.[9] Sexually transmitted diseases are associated with the risk of ectopic pregnancy and infertility. In an American study on 120 postmenarchal adolescent women, 57% of whom were sexually active but had no symptoms, *Chlamydia trachomatis* was identified in one in five.[10] Finally, HIV is a sexually transmitted disease that is increasing in incidence, and AIDS, resulting from the infection, can arise in both men and women.[11] Although homosexual men currently make up two thirds of the incidence of the epidemic in the western world, the rapid increase in this group is slowing and attention has shifted to drug users because this appears to be one of the main routes of entry into the heterosexual population in addition to bisexual activity. The already apparent increase in the population of new cases that have arisen as a result of heterosexual contact may represent a much larger hidden population of people who are positive for HIV. Risks of HIV infections may be closely related both to the number of actual sexual partners and indirectly to the number of partners their partners may have had It is clearly important from the point of view of reducing the incidence of cervical carcinoma and sexually transmitted disease that the number of partners each person has is minimised and education programmes are aimed at young people before they have established patterns of sexual behaviour.

In both studies of men and women most did not plan first intercourse, so that even if teenagers know about contraception it is unlikely to be used in a situation where they are not expecting intercourse to take place. The findings that those having first intercourse at a later age (>16) and those not recruited by a young teenage pregnancy (that is, those from the comparison group) are more likely to be both initial and continuing users of contraceptives lends weight to the hypothesis that later first intercourse is associated with increased personal responsibility.

Many regretted the young age at which they first had intercourse, realising in retrospect that it had been too soon. An essential part of sex education must be discussion of the implications of a sexual relationship. In becoming sexually experienced young people often believe they are simply conforming to the 'norm'. This is supported by the fact that over three quarters of both sexes in the study group had the impression that at least half their friends were sexually active. Both men and women gave the impression that they thought just under half of their peers would be sexually active by 15 years if they had a partner. The important consideration is not whether the supposition is correct, but rather that the perception that their friends are active might directly or indirectly act as a pressure for them to conform and become sexually active.

Bury, in her review of teenage pregnancy, suggested that there has been a change in cultural attitude over the last two decades with a greater acceptance of premarital sex.[2] She found it hard to quantify the effects of television and advertising on young people's behaviour. She felt, however, 'that the media portrayed sexual intercourse as acceptable in any relationship and as exciting adult behaviour the problems associated with sex rarely being shown or discussed'. Allen asked the teenagers in her study their opinion on the influence of videos and 70% thought it might have affected their attitude to relationships.[3]

There appears to be a dual standard with the parents' attitude towards their sons and daughters. Very few men received teaching from either parent and neither were they supervised to the same extent as their sisters. It would appear that parents are concerned lest their daughters 'get into trouble' but not so much about their sons' sexual activity and responsibility. Inazu and Fox in a study from the United States have shown that where the family discusses sex openly with their children they are less likely to become sexually experienced at an early age.[13]

In this district as in others sex education in school has had a much higher profile over the last few years with both sexes receiving similar education. The curriculum varied considerably between schools, however, and the usefulness and impact did appear to be related in part to the person giving the lesson. Although education about relationships and parenthood has been regarded as increasingly important, very few remembered teaching on these topics. Child care and related courses, which discuss child development and parenthood in some detail, appeared to be largely confined to less academic girls.

Various suggestions have been made as to how sex education can be made more effective, these have included: embedding sex education in the core curriculum so that it is covered in a number of different subjects, for example, biology, PSM, English, and therefore studied from a number of different angles[14]; using a spiral curriculum so that the subject is covered in different ways in consecutive years; and using professionals from outside the teaching profession to help schools in this area.[15]

We have not investigated any of these methods formally, but have made some observations:

(1) Many of the teaching staff who are required to teach sex education have had minimal undergraduate or inservice training to equip them in this task and some feel extremely uncomfortable to the extent that pupils are aware of this. Selection of teachers for this important subject should clearly not be based solely on their own main curriculum subject—for example biology or physical education.

(2) Where outside professional staff have been involved and have been selected simply on the basis that they are the allocated school nurse or medical officer similar problems may arise.

(3) Some pupils report considerable enthusiasm for professional input from outside the school staff, and we found that medical facility with terminology and familiarity with the problems teenagers face appeared helpful.

We suggest that the teaching of sex education in schools should be taken very much more seriously both by the teaching, medical, and paramedical professions and that selection to teach this subject should be based on ability, willingness, and enthusiasm as for any other curriculum subject, rather than by default.

This study has shown that many young people are sexually experienced and that many were initiated by an experienced partner who had already had at least one previous partner. The study showed that most men had had several partners and over a quarter of the teenage girls three or more Once involved in a sexual relationship it is almost certain that future relationships will involve intercourse with the possible consequences discussed above

In this study first intercourse had often occurred early, before a 'steady' relationship had been established. Many of those interviewed wished that they had delayed sexual involvement until they had been older. Education at home and school should therefore emphasise the consequences of a sexual relationship and the problems for both partners that can result from early intercourse. Education in the widest sense must help to reduce peer pressure and promote the ways of teaching both sexes in a way that enables them to make decisions which are right for them and will take full account of all the facts and their implications for their own long term future happiness and health. It is our hypothesis that such an educational intervention might result in a number of young people delaying their first experience of sexual intercourse and thus reducing a number of health risks. There are also a number of sociological factors, which have not been discussed in this paper, that suggest that such a delay would be beneficial—for example, in reducing the risk of unwanted pregnancy with its ensuing social disadvantage.

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Family recovery after death of a child

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SUMMARY Children from a national birth cohort living in families in which a sibling had died or been stillborn were compared with children living in similarly structured families where no such tragedy had occurred by a number of health, developmental, and behavioural outcomes. Surprisingly little ill effect from a sibling death (occurring either before or after the birth of study children) was apparent at the age of 5 years. Families experiencing a stillbirth or death of a child were socially disadvantaged. Even allowing for this and other likely intervening factors, however, a child whose adjacent sibling had died was significantly more liable to bronchitis or wheezing during the first 5 years. Mothers who had experienced the death of a child since the study child's birth had high scores on a psychological screening test, and were more likely to be single parents. Mothers who had lost a child were more likely to smoke during the next pregnancy. No significant differences between cases and control subjects were detected on other health, behavioural, or developmental outcomes.

Stillbirth or death of a child appears to have little measurable effect on siblings assessed at 5 years of age. This study does not exclude important longer term psychological effects from sibling death.

Intense parental grieving may follow a stillbirth or the death of a child[1 2]; a mother's reaction in such circumstances seems to be as strong as that of a newly bereaved widow.[3] Surviving children may be severely affected by the death of a sibling,[4-8] and children conceived subsequently have been reported to be liable to a range of adverse behaviour, including overprotection or rejection. [9 10]

Death in childhood is rare in developed societies, even perinatal deaths are uncommon, and becoming fewer. Perinatal and childhood mortality, however, is higher in socially disadvantaged families[11 12], observations in bereaved families, including children's reactions, may be biased by this fact. None of the studies reporting the effects of the death of a sibling on a child have attempted to control for social factors, and most reflect the experience of specialised units that may give unrepresentative views of families' reactions. A total population survey should provide more generally applicable conclusions.

In the present study of a national cohort of British children born in 1970 we have assessed the effect of sibling death on surviving children, and those conceived subsequently, at the age of 5 years, making allowances for likely confounding social and environmental factors

Subjects and methods

The Child Health and Educational Study (CHES)[13 14] is a continuing longitudinal survey of children studied in the neonatal period in the British Births Survey.[12 15] The cohort originally included all the children born in the United Kingdom during 5–11 April 1970. In 1975 children born in that week and living in England, Scotland, and Wales were traced; 12 743 subjects were studied out of a possible 16 015 from the birth survey (79·6%). When the parents were interviewed at home five years after the original survey health visitors gave them specially designed development and behavioural tests and gathered over 500 items of social, family, and health data. The study population for the present analyses comprised those 12 246 children who were singleton births living with their natural mothers at the time of the five year survey.

From the history, families were identified in which at least one sibling of the study child had been stillborn or had died in childhood. Sibling deaths occurring before the birth of the study child were identified at the interview at birth, and subsequent deaths at the five year interview. The information was recorded as either stillbirths and deaths in the

Table 1 *Details of the family structures of the study and control groups*

	Group 1		*Group 2*		*Group 3*	
	Sibling death No (%)	*Control No (%)*	*Sibling death No (%)*	*Control No (%)*	*Sibling death No (%)*	*Control No (%)*
No of older live siblings						
0	13 (2·9)	0 (0·0)	121 (46·4)	0 (0·0)	76 (62·3)	2989 (64·4)
1	143 (32·0)	0 (0·0)	78 (29·9)	4008 (56·5)	22 (18·0)	1031 (22·2)
2	117 (26·2)	1804 (58·6)	28 (10·7)	1804 (25·5)	13 (10·7)	364 (7·8)
3	77 (17·2)	739 (24·0)	20 (7·7)	739 (10·4)	5 (4·1)	144 (3·1)
4 or more	97 (21·7)	537 (17·4)	14 (5·4)	537 (7·6)	6 (4·9)	112 (2·4)
No of younger live siblings						
0	345 (77·2)	2460 (79·9)	140 (53·6)	5437 (76·7)	67 (54·9)	0 (0·0)
1	86 (19·2)	513 (16·7)	101 (38·7)	1413 (19·9)	48 (39·3)	3952 (85·2)
2 or more	16 (3·6)	107 (3·5)	20 (7·7)	238 (3·4)	7 (5·7)	688 (14·8)
Total	447	3080	261	7088	122	4640

first 7 days or deaths after 7 days. Of the sibling deaths, 70% occurred in the perinatal period.

For comparison, three case and three control groups were formed, the control groups with no childhood deaths having the family structure that would have existed had the sibling not died. Group 1 comprised 447 families in which an older sibling had died before the birth of the study child, with at least one intervening living sibling The 3080 control families comprised all families with at least two children older than the study child and no reported sibling death. Group 2 comprised 261 families in which the next older sibling to the study child had died previously. The 7088 control families had at least one child older than the study child Group 3 comprised 122 families in which the next younger sibling to the study child had died. The 4640 control families had at least one sibling younger than the study child. Data from a fourth group (families with one living sibling born after the CHES child, and then a sibling death) were not analysed as the numbers were too small.

Details of the groups including the numbers of study children and the family structure are shown in table 1, the control groups are not mutually exclusive. The proportions of perinatal and postperinatal deaths were similar in all the study groups. Because there was no other information available about the age of those who died subsequently, the present results combine perinatal deaths and those occurring later in childhood; study children who experienced a stillbirth and those who experienced the death of a living sibling were considered together.

The outcomes listed below were assessed,[13] [14] and each group of sibling deaths was compared with the appropriate control population. (1) Problems with excessive crying, feeding difficulties, or disturbances of sleep during the first 6 months of life. (2) At least one episode of wheezing or bronchitis during the first 5 years. (3) The number of admissions to hospital during the first 5 years. (4) The number of accidents requiring medical advice or treatment. (5) The child's height at 5 years (6) An estimate of the child's behaviour by the mother (the Rutter A scale). (7) An estimate of her own psychological state by the mother (the 24 item malaise inventory). The more negative the score, the more depressed, miserable, nervous, or worried was the mother. (8) An assessment of the child's vocabulary (the English picture vocabulary test) (9) An assessment of the child's visuomotor coordination skill.

The variables listed below were collected at the birth or 5 year interviews and were used in the multivariate analyses (logistic multiway contingency table analysis[16] for the discrete outcomes, 1–4 above, and analysis of covariance for the scaled outcomes, 5–9 above). The number of siblings, birth rank, maternal age, the study child's gestational age, maternal smoking during the pregnancy of the study child, whether or not the natural father lived with the family at the time of the 5 year interview, the number of household moves during the child's first 5 years, and the social index (a composite assessment of socioeconomic state derived from indices of domestic crowding, parental education, tenure of accommodation, type of neighbourhood, and father's occupation)[13] at the study child's fifth birthday Where there was missing information on any variable (always less than 5% and for most less than 2%) the subject was omitted from that particular analysis thus the figures in the results exclude missing values

Results

Table 2 shows the differential rates between case and control groups where there were significant differences in the outcomes of the children in any of the study groups Study children who had a younger or older adjacent sibling who died were more liable to lower respiratory symptoms than those in families in which no death had occurred. Early sleeping problems occurred more often in children from families in which an older sibling (with an intervening living sibling) had died or was stillborn. Sleeping problems were no more frequent when it was the next older sibling that had died or was stillborn.

There were no significant differences between children from families in which a sibling had died and children from families with similar structure in which no child had died in assessment of behaviour, vocabulary, visuomotor coordination, height at 5 years, the likelihood of accidents or admission to hospital in early life, and crying or feeding problems during the first 6 months of life.

Though each control group reflects the likely family size and sibling relationships if a death had not occurred in the study group, there are many

Table 2 *Percentage rates of problems or illnesses during the first 5 years of life in which significant differences were found between sibling death and control groups Figures in parentheses are those obtained after adjustment for intervening variables in logistic multiway contingency table analysis*

	Group 1			*Group 2*			*Group 3*		
	Sibling death		*Control*	*Sibling death*		*Control*	*Sibling death*		*Control*
Sleeping problems in first 6 months	12·8 (13·1	* *	9·6 9·7)	13·9		11·2	9·8		15·5
Bronchitis	19·6		18·5	23·6 (22·5	* NS	17·4 18·3)	26·4 (26·1	** **	15·9 15·6)
Wheezing	21·4		20·7	27·1 (26·1	** *	19·9 19·9)	24·2		17·9
Total No	447		3080	261		7088	122		4640

*p<0·05, **p<0·01, ***p<0·001, percentages exclude those with missing results

Table 3 *Percentage differences in social factors between sibling death and control groups*

	Group 1			*Group 2*			*Group 3*		
	Sibling death		*Control*	*Sibling death*		*Control*	*Sibling death*		*Control*
Social index:		***			***				**
Advantaged	8·3		25·8	24·1		35·1	30·3		36·9
Average	45·6		38·1	34·9		37·5	27·1		35·7
Disadvantaged	46·1		36·1	41·0		27·4	42·6		27·4
Mother smoked during pregnancy	52·8		51·4	60·5	***	48·3	54·9		48·9
No father at 5 years	9·4		7·7	7·7		7·1	14·8	**	6·6
Mother aged <20 years at study child's birth	0·0		0·4	2·7		2·4	19·3		14·6
Household moves during first 5 years:									
Nil	58·6		53·3	52·3		49·2	26·4		35·2
2 or more	24·2		13·8	19·0		16·1	33·1		26·8
No maternal educational qualifications	73·6	*	67·7	68·7	**	58·4	65·0		54·4
Total No	447		3080	261		7088	122		4640

*p<0·05, **p<0·01, ***p<0·001 percentages exclude those with missing results

Table 4 *Standardised scores for maternal malaise*

Mean maternal malaise score	*Group 1*		*Group 2*		*Group 3*		
	Sibling death	*Controls*	*Sibling death*	*Controls*	*Sibling death*		*Controls*
Unadjusted	−0·19	−0·11	−0·05	−0·00	−0·34	***	−0·03
Adjusted					−0·26	**	−0·03

***p<0·001, **p<0·01, unadjusted results are shown together with those obtained after allowing for intervening factors in an analysis of covariance for the one result with a significant difference between cases and controls on the unadjusted results

other social, environmental, and possibly biological influences that should be considered before concluding that observed problems do result from an event such as a sibling death. Table 3 shows the distribution of the various social factors considered for each group. Families who experienced the death of a child were socioeconomically disadvantaged compared with their controls. The mothers of children with a dead older sibling were less likely to have any educational qualifications, and those whose child immediately before the study child had died were more likely to have smoked during the pregnancy of the study child. Families in which a sibling younger than the study child had died were more likely than their controls to be without a father figure when the study child was 5 years old.

The results when these possible confounding factors were taken into consideration in multivariate analyses are shown in parentheses in table 2. The marginally significant associations with early sleeping problems were unaffected, but the signficance of the associations with bronchitis and wheezing were attenuated. The most important associations with lower respiratory symptoms were maternal smoking during pregnancy and the social index ($p<0·001$ for both, even allowing for possible intervening factors).

The effect of a child's death on the mother's psychological state assessed by the malaise scale is shown in table 4, with unadjusted results for the sibling death groups and their controls together with the results when intervening factors were considered in an analysis of covariance. Mothers who had recently lost a young child were likely to have high scores, significantly different from controls (with only slight attenuation after allowing for intervening variables). There was no signficant association between maternal malaise score and sibling death in groups 1 and 2.

Discussion

Several previous studies have investigated children's reactions to the death of a sibling, or the effects on a child subsequently born into a family where a child has died or been stillborn. These have taken the form of assertions based on individual professionals' experiences,[7 9] uncontrolled studies of children following the sudden death of a sibling in infancy,[6] or from cancer,[8] and case reports of children with behaviour problems,[4] and of adults with psychiatric disorders.[5]

The present study used data about children from a large national cohort who were selected only by week of birth—that is, a total population. This approach is strengthened by the wide range of background social, birth, and health information that can be taken into account when estimating the effect of the death of a sibling on the health, behaviour, and development of the child, and on the mother's state of mind. This study set out to look for the effects of possible confounding factors on a child's reaction to the death of a sibling. Our results confirm the strong association between death in childhood and social disadvantage, and highlight the importance of taking such factors into account when assessing the effects of death in childhood on families.

The three groups of families with dead siblings gave three different viewpoints of the effect of a death in childhood. The families in group 3 (where the adjacent younger sibling had died) included some where the death was a relatively recent event. As a group, these families were socially disadvantaged (table 3), the mothers were more likely to be unsupported by a father figure in the home when the study children were 5 years old, and their malaise scores were significantly higher than those of mothers in control families. The malaise is not wholly explained by social disadvantage, and seems likely to reflect the recent death of a child. The only other positive finding in this group was a higher incidence of bronchitis in the first 5 years.

In those families in which the next older child had died (group 2), most of the deaths occurred before the birth of the study child, the majority in the perinatal period Maternal malaise was no longer evident, but these families were socially disadvantaged (table 3), and the mothers had fewer educational qualifications compared with the control group. The increased rate of maternal smoking during the pregnancy of the study child when the next older sibling had died is an ironic finding. Women's awareness of the adverse effects of smoking in pregnancy and on their children's health was probably not great in 1970. Smoking in pregnancy and socioeconomic disadvantage are two major predisposing factors to bronchitis and wheezing in the first 5 years.[17] [18] Even allowing for these and other possible intervening variables, however, the death of a sibling seemed to have made a significant contribution in the present analysis The related stress in the family may be an explanation.[14]

Children in families where a distant older sibling had died (group 1) were no different from controls except that they had a higher incidence of sleeping problems in the first 6 months of life. This finding was only evident in this group; possibly when she was interviewed after a long interval a mother who had experienced a child dying might recall sleeping problems in her surviving child as a manifestation of her concern that that child might also die.

The control groups were chosen to reflect the family composition that would have existed had not a sibling died. In group 3 the numbers of living older siblings in the sibling death and control groups were similar (table 1) suggesting that family size in both the study and control groups was similar. An alternative set of controls (those with the family structure pertaining after the death of a sibling) was also examined; similar results were obtained to those presented in this study.

The family composition of the control groups suggests that families who lost children did attempt to 'replace' them. In group 3, in which the deaths had occurred comparatively recently, the family size (excluding the dead sibling) was smaller than that of controls (table 1). In group 1, where the death had occurred some years earlier, the difference in family size between families where the death had occurred and controls was much smaller. The common absence of father figures in families in group 3 where a recent death had occurred suggests that one consequence of such an event may be the break up of the existing parental relationship Presumably a further relationship then develops, accounting for the presence of father figures in the families in groups 1 and 2.

Important specific negative findings in our study include the lack of increased rates of early hospital admissions, accidents, and management problems (crying or feeding in the first 6 months), as well as no obvious effect on the child's growth, development, or behaviour at the age of 5 years. Our results do not support the suggestion that families are likely to move house after the death of an infant.[6]

There are obvious limitations to our conclusions. The CHES population studied at five years was only about 80% of the possible total from the birth study. Those not studied at five years were disproportionally disadvantaged.[13] [14] Children with sibling deaths in these 'missing' families may have exhibited more effects.

Because of the way the data were collected, we were unable to exclude possible effects when an older child dies such a sibling is likely to have been a longer term companion to the study child and an established family member. Only about 30% of the siblings died after the age of 7 days and it is probable that most of these would have been 'cot deaths'. Thus it is likely that most study children would have had only expectant or transitory contact with their dead siblings. Many of the dead siblings would have died either without an illness, or after only a brief illness; a longer illness might increase the grief reaction in siblings.

Both stillbirth and death in childhood used to be commonplace in this country, and still are in many parts of the world. We believe that our findings support the contention that families usually adapt and adjust to the loss of an infant Our results, however, only apply to groups, individual families may be devastated by a child's death. We stress the need for adequate support for bereaved families especially in view of the finding that doctors know less remember less, and seem to be able to think less about mothers who have delivered a stillborn baby.[1] The study children might also have had grieving reactions that we could not assess, and we cannot exclude behavioural or psychiatric problems later in childhood or in adult life

We conclude that the stillbirth or death of a newborn baby or child has little measurable effect (apart from an increased incidence of wheezing and bronchitis in those immediately before or next born) on the health, behaviour, growth, and development of siblings at the age of 5 in this study population, and using the variables included in the present analyses. We confirm the strong association between stillborn and childhood death, and social disadvantage.

There were measurable early effects on the mother's malaise, an apparent increased likelihood of break up of the existing marriage or relationship, an increased incidence of maternal smoking during the next pregnancy, and eventually the adjustment of family size to compensate for the loss The finding of an increase in sleeping problems in the first 6 months probably reflects the bias of intervening major family events on the mother's memory. The overall lack of outward effects on the health of other siblings in this study should not discourage professionals from the important task of providing appropriate support for parents and families after a stillbirth or the death of a child.

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Failure of intraventricular gammaglobulin and α interferon for persistent encephalitis in congenital hypogammaglobulinaemia

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SUMMARY A boy with congenital hypogammaglobulinaemia died at the age of 12 years after a viral meningoencephalitis of two and a half years duration due to an untypable picornavirus. He had received intravenous immunoglobulin every four weeks from the time of the start of immunoglobulin replacement treatment at the age of 3 years. The encephalitis did not respond to high dose intravenous gammaglobulin (2500 g during 22 months). The virus could not be isolated during the administration of intraventricular immunoglobulin (38·15 g) and intraventricular recombinant α interferon (121×10^6 units), but recurred rapidly each time intraventricular treatment was stopped. Further modes of treatment are still required for prevention and treatment of this disorder.

Persisting meningoencephalitis, usually fatal, has been described previously in patients with hypogammaglobulinaemia This disorder has occurred most often in sex linked agammaglobulinaemia, and has commonly been due to infection with echoviruses. Other enteroviruses cause similar infections in sex linked agammaglobulinaemia, however, and vaccine associated poliomyelitis[1 2] and Coxsackie B3 meningoencephalitis[3] have been described In contrast, persisting meningoencephalitis is rare in late onset primary hypogammaglobulinaemia, although fatal measles encephalitis has been reported in an adult with this condition,[4] and one patient with late onset hypogammaglobulinaemia died of meningoencephalitis due to infection with echovirus 11[5]

Standard intramuscular immunoglobulin replacement treatment has not prevented the development of meningoencephalitis In the absence of effective antimicrobial agents for viruses belonging to the enterovirus group, treatment has been directed towards administration of specific antibody either systemically or directly into the central nervous system. There have been reports of apparent remission after high dose intravenous immunoglobulin,[6] infusions of specific antibody containing plasma,[7] and administration of intraventricular immunoglobulin.[3]

This report describes the use of very high dose intravenous immunoglobulin, intraventricular immunoglobulin, and intraventricular recombinant α interferon in a boy with congenital hypogammaglobulinaemia who developed a viral meningoencephalitis due to an as yet untyped picornavirus. Although virus could not be isolated from cerebrospinal fluid during intraventricular administration of immunoglobulin and recombinant α interferon alone and in combination, viral shedding recurred rapidly each time intraventricular treatment was stopped and ultimately his infection was fatal.

Case report

The patient, a boy born in 1974, had recurrent diarrhoea, several episodes of otitis media associated with an aural discharge, and recurrent lower respiratory tract infections from the age of 6 months. Immunological assessment at 3 years of age showed absent tonsils, hypogammaglobulinaemia (IgA, IgM, and IgE not detectable, IgG 1·55 g/l) and absent peripheral blood B cells as determined by surface membrane immunoglobulin bearing lymphocytes. There were no detectable isohaemagglutinins in his serum (blood group A) Polymorphonuclear cell metabolic function was normal, as were his peripheral blood lymphocyte responses to phytohaemagglutinin, pokeweed mitogen, concanavalin A, and allogeneic cells. Peripheral blood T lymphocyte numbers as determined by sheep red cell rosettes were 59%. There was no family history of affected males among maternal relatives.

Treatment with intravenous immunoglobulin was started at the time of diagnosis and he received 4–5 ml/kg of a 6% preparation (240–300 mg/kg) (Commonwealth Serum Laboratories) at intervals of four weeks. He remained in excellent health during the next five years. The median serum IgG concentration immediately before immunoglobulin infusions during his eighth year of life was 2·78 g/l.

At 8½ years of age he had an illness during which he had vomiting and occasional headaches for 10 days. At 9 years his mother noted a slight mood change; at 9½ years he developed horizontal nystagmus. Cerebrospinal fluid was examined and showed a raised protein concentration and a mild leucocytosis. A picornavirus was isolated on culture of the cerebrospinal fluid but was not detected in faeces.

The nystagmus persisted and he developed bilateral sensorineural deafness necessitating the use of hearing aids. Psychometric assessments showed defects in short term auditory memory, a discrepancy between verbal and performance scores by the Wechsler Intelligence Scale for Children, and reduced immediate visual memory. At 10 years of age he developed spontaneous bilateral subdural effusions which were drained.

After viral isolation from the initial sample of cerebrospinal fluid at 9½ years, he started high dose intravenous immunoglobulin treatment (figure). For 22 months he received 200 ml of intravenous immunoglobulin two times a week (1 g/kg/week). The immunoglobulin used had neutralising antibody activity against 30 TCD$_{50}$ (30 times the tissue culture dilution 50% end point) of the virus ranging from 1:8 to 1:32. Serum from family members was tested against his viral isolates and his father's serum was shown to have a neutralising titre of 1:32. Plasma was obtained from his father on two occasions by plasmapheresis, and the patient received 100 ml of plasma by intravenous infusion each week for two five week treatment periods. Transfer factor was prepared from his father's lymphocytes and was given weekly in conjunction with the plasma infusions.

Virus was not recovered from lumbar samples of cerebrospinal fluid taken during the six months after initial viral isolation, but was detected again in it three weeks after his last plasma infusion. Serum from 300 blood donors chosen at random was screened for neutralising antibodies to the virus isolated. The 11 donors with titres of >1:16 had plasmapheresis performed. An IgG preparation manufactured from this plasma pool was given into his left lateral cerebral ventricle through a Rickham reservoir. The IgG had neutralising antibody activ-

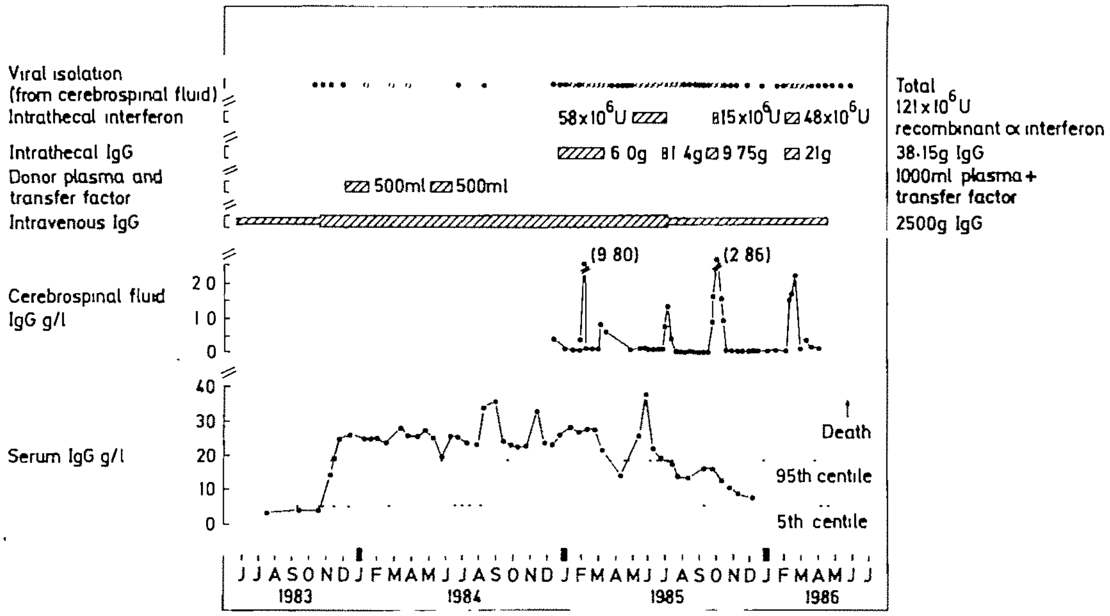

Figure *Viral isolation, intrathecal treatment, and serum and cerebrospinal fluid IgG concentrations in the patient over the three years before death. Closed circles represent samples of cerebrospinal fluid from which virus was isolated, open circles represent samples from which virus was not recovered* ity against 10 TCD$_{50}$ of the virus of a titre of >1:160. and was given twice weekly for 10 weeks. The total dose administered during the 10 week treatment period was 6 g of IgG. Virus recovery from ventricular cerebrospinal fluid stopped after four weeks of treatment, but recurred four weeks after stopping the intraventricular treatment.

Recombinant α interferon was donated by Roche Products Proprietary Ltd, and caused a three log reduction in viral plaque formation in in vitro assays using the virus isolated from the patient's cerebrospinal fluid. He initially received 58×10^6 units of recombinant α interferon by the ventricular reservoir. This was given over a 10 week period, with injections being given three times weekly for nine weeks, and daily in conjunction with 240 mg of intraventricular immunoglobulin for six days during the 10th week. Virus was no longer detected in ventricular cerebrospinal fluid after two weeks of treatment but was reisolated two weeks after it was stopped.

Intraventricular Sandoglobulin was then started and was given daily for two weeks; the total dose administered was 9·75 g. During the last five days of this treatment the patient was also given 3×10^6 units of recombinant α interferon daily by the intraventricular route. Virus could not be isolated from the ventricular cerebrospinal fluid 24 hours after the start of treatment but was reisolated two weeks after it was stopped.

Intravenous immunoglobulin administration was decreased to 200 ml weekly in July 1985 at the age of 11 years He became more lethargic, but continued to attend school. He received further daily intraventricular recombinant α interferon and daily intraventricular Sandoglobulin for three weeks, the total doses administered were 48×10^6 units and 21 g respectively. Virus isolation stopped within 48 hours of starting treatment but his ventricular cerebrospinal fluid yielded virus again two weeks after treatment was stopped. His nystagmus worsened, he developed a transient hemiparesis and paraesthesiae, became ataxic and lethargic, and then developed urinary retention and faecal incontinence. Convulsions occurred, all active treatment was stopped and he died at the age of 12 years.

Discussion

The features in this patient of hypogammaglobulinaemia and a slowly progressive meningoencephalitis characterised by sensorineural deafness, deterioration in higher cerebral function, subdural effusions, transient hemiparesis and paraesthesiae, and convulsions are similar to those described by others. Most such patients have been shown to be infected with echoviruses of varying serotypes, although viral isolation has been difficult in some patients. The patient reported here did not have an associated dermatomyositis like illness.

The virus isolated from his cerebrospinal fluid was characterised as a picornavirus on the basis of its appearance on electron microscopy, resistance to ether, and the nature of the cytopathic effect on primary monkey kidney cells and in diploid human fibroblasts. An unusual feature was its inability to grow in HeLa cells. The virus, however, was not able to be typed as being one of the common echovirus strains. Even at low infective doses of 10 to 30 TCD$_{50}$ the virus was not neutralised by antisera to all common echoviruses, to Coxsackie B1-B6 or to polioviruses. Antisera to Coxsackie A viruses were not available but the inability to grow first passage virus in suckling mice suggest it is unlikely that the virus belongs to this group.

Growth of the virus in continuous monkey kidney cells of the MA-104 line produced two discrete plaque sizes of 1–2 mm and 5–6 mm. Sublines of virus from representative plaque isolates were tested with the above antisera but no neutralisation occurred. Rabbit antisera raised to each of the sublines reacted equally well with the heterologous subline, but neither antiserum neutralised stock cultures of available enteroviruses. It is likely that the variations in plaque size represent genetic variation in a single strain rather than the presence of two separate viruses These points are being investigated further.

Three recent reports have described at least temporary resolution of symptoms, and cessation of viral isolation, after varying routes of administration of relatively high antibody titre immunoglobulin or plasma preparations to infected patients with primary hypogammaglobulinaemia[6 7 9] Prentice *et al* have reported an adult male with sex linked hypogammaglobulinaemia and central nervous system infection with echovirus type 3 who improved clinically while receiving second weekly infusions of plasma, the plasma having a neutralising titre against his echovirus of 1:64 and 1:128 when tested on two different occasions.[7] A further adult patient with X linked agammaglobulinaemia and echovirus 11 meningoencephalitis had prolonged remission of his disease after treatment with high dose intravenous immunoglobulin.[6] Viral shedding recurred when the immunoglobulin was stopped. His condition improved with further intravenous immunoglobulin but recurred when the immunoglobulin infusions were extended from three weekly to four weekly intervals.[9] Remission was achieved by giving 300 mg of immunoglobulin per kilogram every three weeks and was then maintained until the time of reporting two and a half years later.

Recently Erlendsson *et al* reported their treatment of a boy with X linked hypogammaglobulinaemia with meningoencephalitis from whom echovirus type 5 was isolated at the age of 3 years.[8] He failed to respond to intravenous immunoglobulin with a titre of antibody to echovirus 5 of 1:32 given at weekly intervals, but when 138 mg of immunoglobulin was given directly into his cerebral ventricles over five days the virus could not be cultured for two months. After reappearance of the virus in his cerebrospinal fluid he received a further 5·6 g of intraventricular immunoglobulin and he has remained well. The same report described a 12 year old girl with echovirus 25 encephalitis treated in similar fashion who had not had virus cultured from her cerebrospinal fluid during the next 16 months.

There have been several reports of unsuccessful treatment with specific antibodies and with intraventricular immunoglobulin. Plasma infusions containing specific antibody have been unsuccessful or only partly successful in at least four patients[10–13]; hyperimmune sheep serum with antibody to echovirus 3 failed to eradicate the virus[14]; and intraventricular immunoglobulin treatment was unsuccessful in two patients.[5,15] In one of the patients failing to respond to intraventricular immunoglobulin, the virus was no longer isolated from ventricular fluid after treatment but treatment had no effect on the patient's progressive course.[5] The second patient received a total of 12·6 g of Sandoglobulin in two courses of intraventricular treatment, but echovirus 11 continued to be isolated from the cerebrospinal fluid.

The patient described in this report received a total of 38·15 g of intraventricular immunoglobulin in four courses of treatment, 1 g being given daily for 21 consecutive days on one occasion. The immunoglobulin administered came from two geographically different donor pools, and on each occasion virus recovery from cerebrospinal fluid stopped during administration but recurred within weeks of stopping the treatment. He had also received 2500 g of intravenous immunoglobulin during 22 months of treatment, without apparent effect on the clinical course of his meningoencephalitis. Thus even extremely high dose treatment with immunoglobulin preparations may be unsuccessful in this condition.

Exogenous interferon may be expected to be beneficial in chronic viral disorders by limiting cellular viral replication and preventing infection of uninfected cells. In addition, recombinant human leucocyte interferon has been shown to augment natural killer cell activity as well as antibody dependent cellular cytotoxicity and monocyte cytotoxicity.[16,17] Systemically administered interferon is prevented by the blood-cerebrospinal fluid barrier from reaching the central nervous system[18] Several investigators have given interferon intrathecally to small numbers of patients with neonatal herpes, multiple sclerosis, or intracranial malignancies, either by the lumbar route[19,20] or by an intraventricular reservoir.[18] Adminstration has in general been well tolerated, although without specific success in the disorders treated The use of intrathecal interferon in the treatment of meningoencephalitis associated with hypogammaglobulinaemia has not been reported previously.

The patient reported here received a total of 121×10^6 units of recombinant α interferon in three courses. An initial subcutaneous test dose of 5000 units was given without apparent adverse reaction; this was followed by intraventricular test doses of 2500 units, 25 000 units, and 250 000 units During the first course of treatment the interferon was increased to 2×10^6 units three times weekly, during the third course he received 3×10^6 units daily into the cerebral ventricles for 16 days. The only side effect noted was progressively increasing drowsiness during each course of treatment, which resolved within one or two days of its completion.

As with the intraventricular immunoglobulin, virus recovery from ventricular cerebrospinal fluid stopped soon after the start of treatment, but recurred within weeks of it stopping. The period of viral eradication was no greater when immunoglobulin and interferon were used in combination than when immunoglobulin was used alone

The failure of these two forms of treatment in this patient accentuate the need for the development of further antiviral agents effective against the picornavirus group of agents before successful treatment of this type of infection can be assured in patients with hypogammaglobulinaema. Some such agents may become available: benzimidazole derivatives have been shown to inhibit multiplication of picornaviruses,[21] and more recently an arildone derivative, WIN 51711, has been shown to have antipicornavirus activity.[22] It is possible that such agents may also have a degree of synergy with interferon (D Tyrell, personal communication). In the absence of effective antiviral chemotherapy, hypogammaglobulinaemic patients who do not respond to intraventricular immunoglobulin treatment may deserve consideration as candidates for bone marrow transplantation in an attempt to provide an adequate immune response to the infecting agent.

We are grateful to Commonwealth Serum Laboratories (Parkville, Australia), Sandoz Australia Proprietary Ltd, and Roche Products Proprietary Ltd, for making their products available to us We also thank Dr K McGrath and the staff of the Red Cross Blood Bank, Melbourne, and Sisters S Wright, J Hall, and H Upton and Drs H

Zehnworth, CRF Richardson and A Tucker for their invaluable help

Treatment of this patient was approved by the Institutional Ethics Committee

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IgG antibodies to Aspergillus fumigatus in cystic fibrosis: a laboratory correlate of disease activity

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SUMMARY Serum was collected from 50 patients with cystic fibrosis, and IgG antibodies to *Aspergillus fumigatus* were measured by enzyme linked immunosorbent assay (ELISA). In addition, total IgE and *Aspergillus* specific IgE antibodies were measured in 41 of the 50. A close association was found between pulmonary function and clinical state, and IgG antibodies to *Aspergillus*. There was no association between pulmonary function or clinical state and IgE antibodies.

It is postulated that in patients with cystic fibrosis, *Aspergillus fumigatus* may contribute to deterioration in pulmonary function by local pathogenicity, or by hypersensitivity mechanisms mediated by IgG.

Pulmonary disease is the major cause of morbidity and mortality among patients with cystic fibrosis. Little is known about pulmonary mucosal defence mechanisms, even in the healthy adult. IgG is known to be the predominant pulmonary immunoglobulin in both adults[1] and children,[2] and IgA is more important in the upper airway. IgG is an efficient fixer of complement, so there is the potential in the lower respiratory tract for IgG hypersensitivity mechanisms to occur if there is immune dysregulation. The most important cause of progressive pulmonary disease in cystic fibrosis is likely to be chronic infection with *Pseudomonas aeruginosa*.[3] Two studies, however, have shown that children with cystic fibrosis and low concentrations of serum IgG had better lung function and general health than age matched children with cystic fibrosis and normal IgG concentrations.[4–5] Overall, patients with cystic fibrosis have higher serum IgG and IgM concentrations than control subjects.[6] It has also been shown that high titres of precipitating antibodies to *P aeruginosa* in patients with cystic fibrosis may be harmful rather than protective.[7–8] Circulating immune complexes are common in cystic fibrosis, and are associated with acute respiratory exacerbations and deteriorating pulmonary function.[9] These features suggest that hypersensitivity mechanisms and increased inflammatory activity may participate in the pulmonary damage Indeed the results of a trial of prednisolone given on alternate days to patients with cystic fibrosis suggested that there was an appreciable delay in deterioration of lung function tests and fewer hospital admissions in the group treated with prednisolone.[10]

The frequency with which *Aspergillus* precipitins are detected in patients with cystic fibrosis varies from 30% to 60%,[11–12] and their number often parallels the severity of pulmonary disease.[13] *A fumigatus* is a ubiquitous fungus, and all lungs are constantly exposed to it. Allergic aspergillosis has been reported in up to 11% of patients with cystic fibrosis,[14] but is rare in normal subjects. This suggests that patients with cystic fibrosis have an abnormal response to *Aspergillus,* and that there may be important abnormalities in mucosal regulation and defence in patients with cystic fibrosis. Unfortunately precipitation in gels is an insensitive, albeit specific, method for the detection of circulating *Aspergillus* antibody. In addition, it is qualitative, not quantitative.

Our aim was to characterise more fully the response to *Aspergillus* in patients with cystic fibrosis, and to relate the findings to their general health and pulmonary function. An ELISA for the detection of serum IgG antibodies to *A fumigatus* that had been developed in our laboratory was therefore applied to the serum of patients with cystic fibrosis. This ELISA gives quantitative results with high sensitivity.

Patients and methods

Serum for assay of IgG antibody to *A fumigatus* was collected from 50 patients with cystic fibrosis as part of their routine annual blood monitoring. A few of the patients had serum collected during an admission to hospital because of exacerbation of their pulmonary disease. Their ages ranged from 2·5 to 29 years. Forty one patients also had total IgE and *Aspergillus* specific IgE measured. As sputum culture for *Aspergillus* is somewhat unreliable, it was not performed. Serum was also collected from 40 age matched patients with mild, episodic asthma to serve as controls. There were insufficient age matched patients with bronchiectasis who did not have cystic fibrosis to act as controls.

For the *Aspergillus* IgG ELISA, the *Aspergillus* antigen was prepared from a commercially available supply (*Aspergillus* somatic antigen, Mercia Brocades). The *Aspergillus* antigen was diluted to 25 μg/ml in sodium carbonate buffer, pH 9·6. Fifty microlitres of the diluted antigen was added to a 96 well, round bottomed, polystyrene, microtitre plate and left at 4°C overnight. There were eight dilutions of each serum starting at 1/15 and diluting three fold from then on—that is, 1/45, 1/135, 1/405, and so on. These dilutions were performed in triplicate in phosphate buffered saline (PBS) containing 0·05% Tween 20 and 0·25% bovine serum albumin (PBS-T-BSA). This was added to the antigen coated plates and incubated for one hour at 37°C, followed by two hours at 4°C. Plates were then washed five times with PBS-T, and 100 μl of alkaline phosphatase labelled antihuman IgG (DAKO) added to each well and incubated for 16 hours at 4°C. Plates were washed five times in PBS-T and 100 μl of a 1 mg/ml solution of p-nitrophenyl phosphate in diethanolamine buffer, pH 9·8, added to each well. After 30 minutes at 37°C the reaction was stopped by adding edetic acid to a final concentration of 40 mM. Absorbance was measured at 405 nm on an automatic ELISA plate reader (Dynatech MR600), and graphs were drawn for each serum. The serum titre was calculated by interpolation of the graphs, and expressed as the serum dilution yielding an optical density of 0·4. ELISA units were calculated by reference to a known positive reference included in each run. This consisted of a pool of seven high titre serum samples in aliquots stored at −80°C. One aliquot was removed and run with each test.

Using the result from the reference aliquot, an ELISA value was given for each sample using the following formula: titre of test serum × 1000/titre of reference serum=ELISA units. The reference samples were arbitrarily assigned a value of 1000 units, and each test sample was compared with this value. The interassay coefficient of variation for this ELISA is 23%, and the intra-assay variation 10·4%. Total serum IgE was measured with the Phadezym IgE PRIST, and *Aspergillus* specific IgE antibodies were measured with Phadezym RAST 60 (Pharmacia Diagnostics AB).

Except for seven patients who were too young, all had pulmonary function tests performed; these were done with the patient standing. Maximum expiratory flow volume curves were obtained with an OHIO 842 spirometer and the curves were displayed on a Hewlett-Packard 7041 A X–Y recorder. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow measured between 25% and 75% of the expired vital capacity (FEF_{25-75}), were derived from the curve. At least three curves were performed for each subject. The results were expressed as a percentage of expected value for height

The general health of the patients was assessed using the Shwachman score, a four way appraisal of health covering general activity, physical examination, nutrition, and chest radiograph.[15]

Pearson correlation coefficients were computed from linear regression analyses. Significance was assessed by reference to standard tables.

Results

All control subjects had undetectable IgG specific antibodies to *A fumigatus*

Overall, 70% of the patients with cystic fibrosis had measureable IgG antibodies to *Aspergillus*. All patients older than 12 years had measurable IgG antibodies (fig. 1). No patient younger than 4 years had detectable antibodies. There was a progressive rise in antibody titres with increasing age (r=0·57, p<0·001). The three patients who died from their

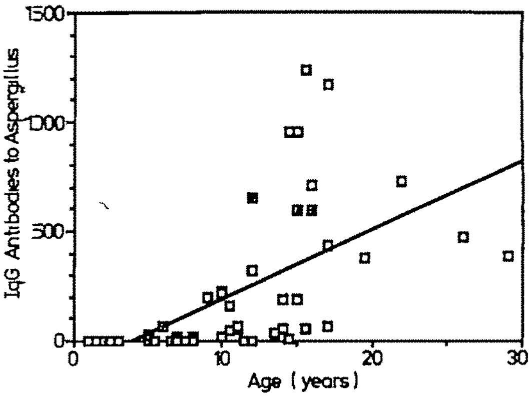

Fig 1 *IgG antibodies to Aspergillus (ELISA units) and age, r=0·57 p<0·001 Some values are concentric.*

disease during the study had IgG antibody titres of 250, 978, and 1198 units.

There was a close correlation between the *Aspergillus* IgG value and the Shwachman score (fig 2). As the Shwachman score deteriorated the *Aspergillus* IgG value increased ($r=-0{\cdot}79$, $p<0{\cdot}001$). All patients with Shwachman scores of less than 70 had detectable antibodies. There was also a close correlation between increasing *Aspergillus* IgG values and deteriorating pulmonary function (figs 3–5). FEV_1 and FEF_{25-75} as % of predicted values showed similar results ($r=-0{\cdot}67$ and $-0{\cdot}68$, $p<0{\cdot}001$). With increasing *Aspergillus* IgG values there was a fall in FVC ($r=-0{\cdot}61$, $p<0{\cdot}001$). All patients with FEF_{25-75} less than 68%, FEV_1 less than 75%, FVC less than 60% of predicted values, had detectable *Aspergillus* IgG antibodies.

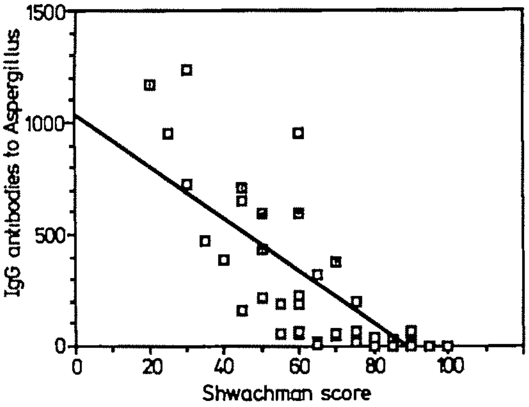

Fig 2 *IgG antibodies to Aspergillus (ELISA units) and Shwachman score; r=−0·79, p<0·001 Some values are concentric.*

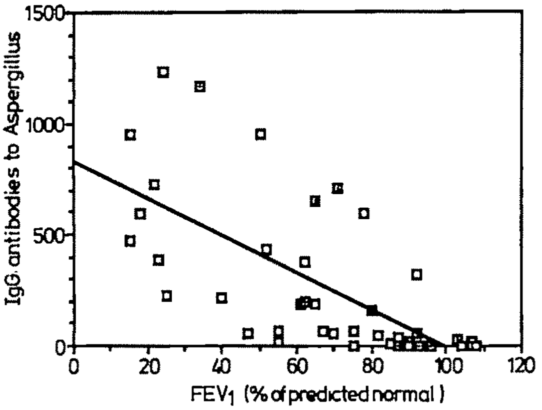

Fig 3 *IgG antibodies to Aspergillus (ELISA units) and FEV₁, r=−0·68, p<0·001. Some values are concentric.*

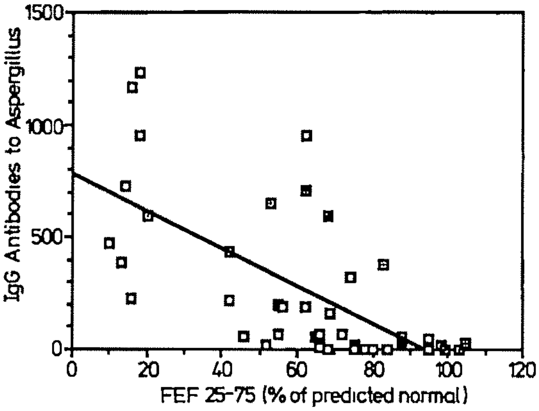

Fig 4 *IgG antibodies to Aspergillus (ELISA units) and FEF25–75. r=−0 67, p<0·001. Some values are concentric*

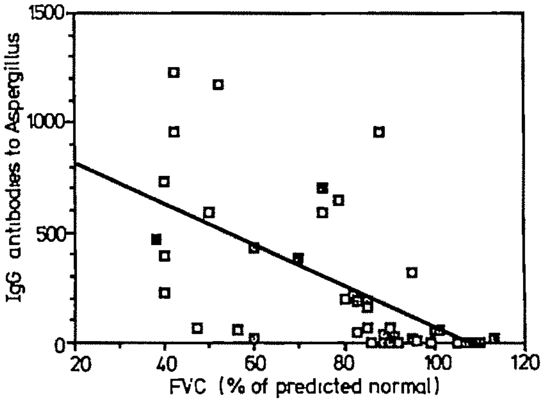

Fig 5 *IgG antibodies to Aspergillus (ELISA units) and FVC. r=−0·61, p<0·001. Some values are concentric*

There was no correlation between *Aspergillus* IgG antibody titres and either *Aspergillus* IgE titres or total IgE. Nine of 47 patients tested (19%) had detectable IgE antibodies to *Aspergillus*, and 10 of 41 (24%) had raised total IgE concentrations.

Discussion

A fumigatus is present in air, soil, animals, plants, and water. It has even been reported in 90% of commercial packages of macaroni, spaghetti, and similar pasta products [16] The isolation of *Aspergillus* in sputum is therefore difficult to interpret Airborne *Aspergillus* can lodge on sputum as it is expectorated or during culture making the assessment of colonisation or infection difficult. Hence, serological evidence of *Aspergillus* is more specific. This fungus can, after inhalation, produce different patterns of respiratory tract infection saprophytic bronchopulmonary aspergillosis (colonisation), aspergilloma (mycetoma or fungus ball), hypersensitivity induced aspergillosis, and invasive pulmonary aspergillosis.[17]

Our finding of IgG antibodies to *Aspergillus* in 70% of patients with cystic fibrosis is the highest reported. That the antibody titre rises with increasing age, falling Shwachman score, and falling respiratory function values, indicates the importance of the fungus in patients with cystic fibrosis. Rising *Aspergillus* IgG values with age indicate progressively more exposure to the fungus, or a progressively aberrant immune reponse. The high serum IgG values in those patients in a poor clinical state (low Shwachman score) presumably reflects a high antigen load presented to the systemic immune system, possibly because of inefficient removal of antigen from diseased, bronchiectatic lungs. That no child younger than 4 years had detectable antibodies might suggest that appreciable anatomical or immunological airway disease becomes established after that age.

The closest correlation with the *Aspergillus* IgG value was the Shwachman score, a measurement of general health. If the severity of lung disease was the measurement most influencing the development of IgG antibodies, we might have expected the correlation between the antibody titre and respiratory function results to have been closer than that between antibody titre and Shwachman score. Limitations in the ELISA or the respiratory function testing, or the influence of other aspects of pulmonary disease may have influenced this result. In addition, the degree of bronchiectasis, mucus plugging, and narrowing of small airways is variable in those dying from cystic fibrosis.[18]

There is evidence that high precipitating antibodies against *P aeruginosa* may be important in exacerbating pulmonary disease through inflammatory mechanisms.[7-9] We found high titres of IgG antibodies to *Aspergillus*, particularly in those with more severe disease. Raised IgG antibody titres in those with more severe disease may simply be due to colonisation of damaged lung. Another possibility is that the high antibody titres might lead to an increase in the amount of inflammation in diseased lungs—for example, through immune complexes and complement activation—contributing to further damage.[9]

Invasive aspergillosis is lethal and requires specific antifungal chemotherapy. Pulmonary invasion is said to occur because of decreased host defences, particularly in neutropenia and leukaemia, with colonisation only occurring in the presence of chronic lung disease.[19] There is some evidence of decreased systemic immunity in cystic fibrosis,[20] and little is known about respiratory mucosal defence. In addition, invasive pulmonary aspergillosis has been reported recently in patients who were neither immunocompromised nor neutropenic.[21] We have established that there is a vigorous response to *Aspergillus*, particularly in those with more severe disease. It is important therefore to ensure that some degree of localised pulmonary invasion by *Aspergillus* is not occurring late in the course of their disease.

Hypersensitivity induced aspergillosis has been reported in 11% of patients with cystic fibrosis.[14] That 19% of our patients had positive RAST scores to *Aspergillus* suggests that a sizeable subgroup of patients with cystic fibrosis may have abnormal immune regulation to this fungus, particularly at the respiratory mucosal surface. As there was no correlation between pulmonary function and *Aspergillus* specific IgE antibodies, however, it is unlikely that mechanisms mediated by IgE are important in most of these patients. Further studies on respiratory mucosal defence and the influence of *Aspergillus* on lung disease in patients with cystic fibrosis are needed. In particular, pharmacological measures aimed at reducing colonisation by *A fumigatus* and hypersensitivity mechanisms, allied to respiratory function testing, might be considered.

In summary, we have described a sensitive method for the detection of IgG antibodies to *Aspergillus*. Patients with cystic fibrosis have high IgG antibody titres to *Aspergillus* that parallel progression of the disease. What contribution if any the fungus makes to pulmonary disease, and what contribution the high IgG antibodies and inflammatory mechanisms make, remain to be established.

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C reactive protein concentrations in cystic fibrosis

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SUMMARY Serum concentrations of C reactive protein were measured in a cross sectional study of 36 patients with cystic fibrosis and correlated with clinical and radiological assessments. C reactive protein concentration was highly correlated with the Shwachman clinical evaluation score, forced vital capacity as a percentage of the predicted value, and the Chrispin-Norman *x* ray score. C reactive protein may be a useful objective index of severity of disease in patients with cystic fibrosis.

C reactive protein is an acute phase protein whose concentration in the serum rises as much as 1000 fold during the acute phase response.[1] A raised concentration of serum C reactive protein is unequivocal evidence of an active tissue damaging process and is related both to the severity of the tissue injury and to the type of inflammatory stimulus. For example, large increases occur frequently in bacterial but not in viral infections.[2 3] Its potential clinical usefulness had been explored in neonatal meningitis, septicaemia, postoperative infections, shunt infections, pyelonephritis, rheumatoid arthritis, and Crohn's disease.[2 4] It has also been advocated as a screening test for bacterial infections in febrile children.[3] We report here on serum C reactive protein concentrations in patients with cystic fibrosis and consider its potential use as an index of the severity of the disease.

Patients and methods

C reactive protein concentrations were measured in patients with cystic fibrosis and healthy children in a cross sectional study over a four month period. Fifty healthy afebrile children (age range 0·03–16·1 years, median: 6·7 years) who were undergoing day surgery (circumcision, eight; herniorraphy, 10; orchidopexy, seven; urethroscopy, three; cystoscopy, four; anal stretch, two; others, 16) were studied to establish a reference range for C reactive protein. A blood sample was taken preoperatively after induction of anaesthesia and C reactive protein was measured quantatively by an enzyme linked immunosorbent assay (ELISA).

Thirty six patients with cystic fibrosis were assessed during either a routine outpatient clinic appointment or an admission to hospital. Each patient was assessed clinically using: (1) Shwachman clinical evaluation score, which is comprised of four categories. general activity, physical examination, general nutrition, and chest radiography findings.[5] A maximum score of 100 points is possible and decreases as the disease worsens. (2) Chrispin-Norman *x* ray score in which the chest radiograph is divided into four zones each of which is scored according to the type of shadows visible on *x* ray.[6] Chest configuration is also assessed. Score increases as the disease worsens to a maximum of 38 points.

If chest radiography of the patient was not clinically indicated at the time of the clinic visit, the most recent chest radiograph taken within six months was scored in order to avoid additional exposure of patients to radiation.

Respiratory function tests: the forced expiratory volume in one second and forced vital capacity, were performed on all patients over 6 years of age using a portable Vitalograph machine (a single breath wedge bellows spirometer, serial no M3799) and expressed as a percentage of the predicted value for age and sex. Peripheral blood was taken for measurement of C reactive protein, white cell count (measured in an electronic Coulter counter), and measurement of the erythrocyte sedimentation rate by the Westergren method.

Spearman's rank correlation was used to determine the statistical relation between C reactive protein on the one hand and Shwachman score, Chrispin-Norman *x* ray score, forced expiratory volume in one second, forced vital capacity, white cell count, and erythrocyte sedimentation rate on the other.

Results

The serum C reactive protein concentrations in healthy children ranged from 0·01–2·8 mg/l. Neither these values nor their corresponding logarithms were normally distributed so the upper 95% confidence limit, 1·875 mg/l, was used as the upper limit of the normal range.

C reactive protein concentrations in patients with cystic fibrosis ranged from 0·01–304 mg/l, and concentrations were above the normal range for healthy children in 30 of 52 samples (20 of 36 patients). Considering only the first specimen taken from each patient, there were high correlation coefficients between C reactive protein on the one hand and Shwachman score ($r=-0·77$; $p<0·001$) (fig 1), Chrispin-Norman *x* ray score ($r=0·68$, $p<0·001$) and forced vital capacity as percentage of predicted ($r=-0·781$; $p<0·01$) on the other. C reactive protein was less closely correlated with forced expiratory volume in one second as percentage of predicted ($r=0·54$). Low correlations were seen between indices of severity of the disease and either white cell count or erythrocyte sedimentation rate. The highest of these was seen between the Shwachman score on the one hand and white cell count ($r=-0·57$) and erythrocyte sedimentation rate ($r=-0·35$) on the other.

Although this was not a longitudinal study, five or more serial measurements were made in two patients during the course of respiratory exacerbations (fig 2). In patient 1, bacterial infection was initially controlled with antibiotic treatment. A period of subsequent clinical stability was then followed by further exacerbation leading to terminal deterioration. Patient 2 had an initial clinical response to antibiotics but required prolonged antibiotic treatment and physiotherapy before returning to his baseline level of respiratory function at the time of clinic review.

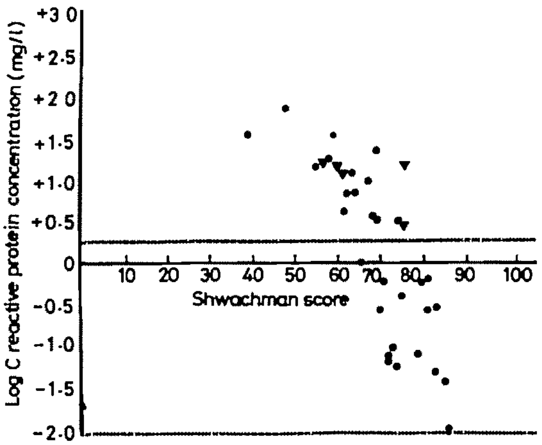

Fig 1 *Log serum C reactive protein concentration (mg/l) plotted against Shwachman score in 52 samples from patients with cystic fibrosis.* ▼ *=Sample taken during an acute exacerbation of a respiratory infection The upper 95% confidence limit for serum C reactive protein concentration in healthy children is indicated by a dotted line.*

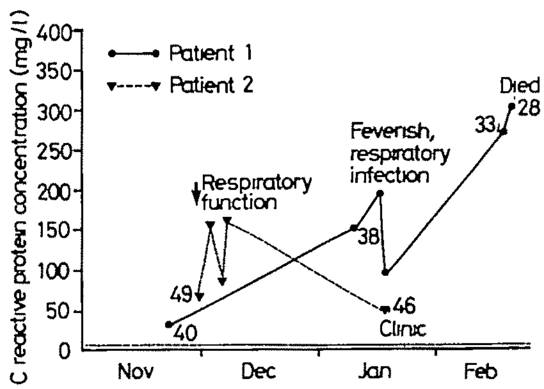

Fig 2 *Serum C reactive protein concentration (mg/l) in two patients with cystic fibrosis. The upper 95% limit for serum C reactive protein concentration in healthy children is indicated by a dotted line Numbers adjacent to plotted points represent simultaneous Shwachman scores*

In both patients, bacterial respiratory infections were accompanied by an increase in C reactive protein concentration and subsequent fall with antibiotic treatment (fig 2).

Discussion

Cystic fibrosis is a condition in which there is progressive bronchopulmonary damage caused by recurrent respiratory infection of which serum C reactive protein concentrations, as yet unreported in these patients, might provide a useful measure. Raised serum concentrations of C reactive protein were seen in 20 of 36 patients with cystic fibrosis in this study including all 25 samples from patients with a Shwachman score of 66 or less. A raised concentration of C reactive protein identified this group with a sensitivity of 100% and specificity of 78%. Typically a patient with a score of 66 would 'tire easily after exertion, have a daily cough, respirations would be slightly elevated, weight and height between 3rd and 10th percentile and the stools abnormal'.[5]

There were highly significant correlations between the serum C reactive protein concentration and both the Shwachman score and the forced vital capacity as a percentage of predicted. As a good correlation between forced vital capacity and clinical and radiological state has previously been shown,[7] a rising C reactive protein appears to be a simple objective index of worsening clinical condition. By contrast, white cell count and erythrocyte sedimentation rate were not useful in this respect in this study. The rank correlation between C reactive protein and the Chrispin-Norman *x* ray score was also high and significant even though it may have been artificially reduced by the use of the most recent chest radiograph rather than one taken on the same day.

As patients with mild symptoms had abnormal concentrations of C reactive protein we suggest that the serum concentrations may be used as an early marker of deterioration in patients with cystic fibrosis who are not yet severely affected. A high serum C reactive protein concentration may signal the need for more aggressive treatment. Furthermore, our limited experience of serial measurements in cystic fibrosis suggests that a raised concentration of C reactive protein that is out of proportion to other measures of progression of the disease is likely to represent a bacterial exacerbation (fig 2). The decline in concentrations of C reactive protein after antibiotic treatment may be useful in monitoring response to treatment in patients with cystic fibrosis in whom this is clinically difficult.[2–4] Serum C reactive protein measurement has already been shown to be useful in monitoring the response to antibiotic treatment in immunosuppressed children.[8] Our results suggest that routine measurement of C reactive protein in cystic fibrosis may be useful and merits longitudinal study.

We thank Drs CJ Rolles, GM Lewis, and MJ Simpkiss for their permission to study their patients and Dr F Stevenson for supervising the ELISA measurements of C reactive protein

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Clinical outcome of fetal uropathy

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SUMMARY Thirty seven infants (27 boys and 10 girls) whose uropathy had been diagnosed antenatally were reviewed at a mean age of 24·4 months. Antenatal ultrasonography was found to be an accurate detector of renal disease, as uropathy was subsequently confirmed in 33 of the 37 infants (89%). A smaller proportion of patients required operations than in other series reported. Shortly after birth the kidney undergoes physiological adjustments and investigation may be carried out too soon. It should be delayed, especially if the infant is well. The timing of postnatal ultrasonography is important and the advice of a paediatric urologist should be sought before investigations are carried out.

More fetal anomalies are being discovered as a result of routine antenatal ultrasonography. The normal urinary tract can be seen as early as the fifteenth week of gestation, and up to 95% of fetal kidneys can be identified by the twenty second week.[1] In recently published series the reported incidence of fetal uropathy diagnosed by antenatal ultrasonography was between 0·14% and 0·39%.[2–7]

The management of uropathy diagnosed antenatally remains a matter of debate; in the series reported there has been a variable but high incidence of surgical intervention (46–80%).[6–8]

Patients and methods

Over a six year period (1981–7) 37 infants (27 boys and 10 girls) in whom an antenatal diagnosis of uropathy was made were referred to this centre, which serves south and mid Wales. During the first two years of the study only one infant was referred; the referral rate at the time of writing had increased to one infant every three weeks, which represents about 0·1% of live births. This is almost certainly an underestimate because antenatal ultrasonography is not routinely performed in the whole of our catchment area.

In all the infants the diagnosis was made in the third trimester when ultrasonography was performed for obstetric indications. One infant was delivered at 38 weeks' gestation by emergency caesarean section performed for fetal distress; all other infants were delivered normally.

The infants were referred after postnatal ultrasonography. Some of them had had other investigations including intravenous urography, isotope renography, or micturating cystourethrography, performed before referral. Postnatal ultrasonography was performed at this centre using a real time mechanical sector scanner (Technicare Autosector MCU) with a 5 or 7·5 MHz transducer.

Results

The 37 infants can be divided into two groups according to the antenatal diagnosis—unilateral uropathy (n=25) and bilateral uropathy (n=12) (tables 1 and 2). Oligohydramnios was not reported on any of the scans.

In 33 infants the presence of uropathy was confirmed, in two there was a non-renal lesion that had produced confusing ultrasonographic signs (unilateral suprarenal haematoma in one infant and duodenal diaphragm in the other), and in only two infants was there no lesion. An accurate diagnosis was therefore made in 89% of cases. Thirteen of the 33 infants required operations

Pyeloplasty was indicated in three of the 15 infants with obstruction of the pelviureteric junction. There was objective evidence of deterioration (unremitting gross hydronephrosis and worsening differential function on isotope renography). Operations were performed at a mean age of 16·7 months. Improving function was the indication for continued conservative management in the other 12 infants.

Of the seven infants with obstruction of the vesicoureteric junction two required reimplantation of the ureters, one underwent reimplantation and contralateral removal of a cystic dysplastic kidney

Table 1 *Postnatal diagnoses and treatment in 25 patients in whom antenatal ultrasonography had shown unilateral uropathy*

Postnatal diagnosis	*No*	*No needing operation*
Unilateral obstruction of pelviureteric junction	11	Pyeloplasty (2)
Bilateral duplex kidneys, unilateral hydronephrotic upper moiety, and ureterocele	1	Ureteroplasty (1)
Unilateral duplex kidney with dilated lower moiety	1	None
Bilateral vesicoureteric reflux	1	None
Unilateral obstruction of vesicoureteric junction	2	None
Bilateral obstruction of vesicoureteric junction	1	None
Cystic dysplasia	6	Nephrectomy (6)
Normal kidneys and duodenal diaphragm	1	None
Normal kidneys and unilateral adrenal haematoma	1	None

Table 2 *Postnatal diagnoses and treatment in 12 patients in whom antenatal ultrasonography had shown bilateral uropathy*

Postnatal diagnosis	*No*	*No needing operation*
Bilateral obstruction of pelviureteric junction	4	Unilateral pyeloplasty (1)
Bilateral vesicoureteric reflux	1	None
Bilateral obstruction of vesicoureteric junction	3	Bilateral reimplantation of ureters (1)
Cystic dysplastic kidney with contralateral obstruction of vesicoureteric junction	1	Unilateral nephrectomy and reimplantation of ureter (1)
Bilateral ureterocoeles	1	Bilateral ureteric meatotomy (1)
Normal kidneys	2	None

at the age of 2 months, and the other had bilateral reimplantation of the ureters at the age of 6 months. Function improved in the remaining five patients. Both patients with bilateral vesicoureteric reflux were treated conservatively. Nephrectomy was performed in seven patients with cystic dysplastic kidneys at a mean age of 10 months.

At the time of writing all 37 patients are well and thriving at a mean age of 24·4 months (range 5–90 months).

Discussion

In the presence of normal volumes of amniotic fluid, renal and pulmonary function is usually normal, whereas in the presence of oligohydramnios the prognosis is poor.[9] Because renal dysplasia is well advanced by the time of the first ultrasound scan (which is usually performed at 12–16 weeks' gestation) the argument for treatment by antenatal drainage is untenable.[10] The role of antenatal drainage is still a matter for debate, but it may have a role in the management of infravesical obstruction in the presence of a normal volume of amniotic fluid.

The fetus with bilateral hydronephrosis who presents with oligohydramnios before the twentieth week of gestation is likely to have poor renal function.[9]

Bilateral hydronephrosis in the presence of a normal volume of amniotic fluid should be followed up by serial ultrasonography for the remainder of the pregnancy. It may be appropriate to induce labour early if there seems to be progressive deterioration of fetal renal function (which remains difficult to assess). The volume of amniotic fluid provides an indirect assessment of fetal renal function.

Measurement of the fetal transverse thoracic diameter provides evidence of impaired renal and pulmonary function.[11] The fetal bladder volume can be measured after administration of intravenous frusemide to the mother (frusemide stimulation test).[12]

No action is necessary for a unilateral lesion and a normal contralateral kidney. Pelvicalyceal dilatation may be transient and subsequent postnatal investigations may be entirely normal.[11]

The natural history of obstruction to the pelviureteric and vesicoureteric junctions is unknown, and investigation showed continuing improvement and regression of abnormal signs in most cases; early operation is only indicated in a few. Careful follow up enables us to justify our conservative policy.

In the series reported by Smith *et al*, 12 of 15 patients (80%) required operations for uropathy within the first year of life.[6] In that reported by Thom *et al*, 16 of 35 patients (46%) required operations during infancy.[7] Turnock *et al* reported 20 of 29 patients (69%) who required operations, 14 of them during the first month of life.[8] Of our 33 patients only 13 (39%) have required operations over a longer period (to a mean age of 25·6 months).

The kidneys start to excrete urine by the tenth week of gestation but fluid balance is primarily regulated by the placenta. Immediately after birth the neonate is comparatively dehydrated because of a reduced intake of fluid and inability to concentrate urine. Lowered perfusion pressure and high vascular resistance result in a low glomerular filtration rate. In the first 12 hours of life the glomerular filtration rate is approximately 15% of the adult, and doubles to 30% by the age of two weeks. The lowered glomerular filtration rate and comparative dehydration may result in diminished filling of a dilated pelvicalyceal system. Ultrasonography performed within a few hours of birth may therefore fail to confirm the antenatal diagnosis of pelvicalyceal dilatation[13] For this reason postnatal ultrasonography should be delayed until the neonate is at least 24 hours of age. As a result of the lowered glomerular filtration rate, intravenous urography and isotope renography performed within a few days of birth are often unsatisfactory and of little diagnostic help.

Antenatal ultrasonography is a good detector of uropathy but is comparatively bad at providing the exact diagnosis of specific lesions. Operation is indicated in only a few of these infants, and appropriate postnatal investigation enables them to be identified. We believe that the infants in this study would not have presented at birth if antenatal ultrasonography had not been performed. Antenatal ultrasonography seems to have been most beneficial to two groups, infants with obstructive lesions who required operations and infants with vesicoureteric reflux. In both groups postnatal renal damage was minimised because the uropathy had been identified by antenatal ultrasonography resulting in appropriate postnatal investigation and management.

We recommend that all cases of infravesical obstruction be discussed with a paediatric urologist when the antenatal diagnosis is made and certainly before delivery. Others should have postnatal scans after the age of 24 hours and should then be referred.

We thank the paediatricians who referred their patients and the radiologists who performed the initial investigations

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Technical editor's note

From January 1989 results and measurements in the *Archives of Disease in Childhood* will be given in SI units only. Would contributors please ensure that all results in manuscripts, tables, and figures submitted from now on are in SI units otherwise publication may be delayed. Exceptions to this are:

(a) Blood pressure in mm Hg;
(b) Ventilation pressure in cm H_2O;
(c) Concentration of drugs;
(d) Concentration of any substance where the molecular weight is not known accurately.

No old units or conversion factors should be submitted in manuscripts: conversion is the responsibility solely of the author.

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Short reports

Inner city tuberculosis and immunisation policy

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SUMMARY Asian children, excluding recently arrived immigrants, had a similar incidence of tuberculosis to white children in Leeds from 1982–6. Children living in the urban priority area were 2·6 times more likely to develop tuberculosis than those living elsewhere. Selection for infant BCG immunisation should not depend on ethnic group alone.

The tuberculosis notification rate in 1983 for children born in the United Kingdom was 29 per 100 000 for children of Indian ethnic origin and 50 per 100 000 for those of Pakistani or Bangladeshi origin.[1] It is the practice in Leeds, as in other British cities, to offer BCG immunisation to infants of Asian origin. All children with tuberculosis, and all those receiving antituberculous chemoprophylaxis from 1982–6 were studied to determine the epidemiological pattern of the disease in relation to current immunisation policy.

Methods

Case notes were examined for all children from Leeds metropolitan district (total population 710 000) aged 14 years or less who started treatment for active tuberculosis or received antituberculous chemoprophylaxis after contact with tuberculosis during the five year period January 1982 to December 1986. Records were obtained from the Leeds chest clinic and local hospitals Notifications to the medical officer (environmental health) and patients identified by hospital activity analysis were traced to ensure that no cases had been missed.

Children who were new immigrants, including one Bangladeshi boy with active disease and seven receiving chemoprophylaxis (six of whom were from the Indian subcontinent), were excluded from the study. All children included in the study had either been born in the United Kingdom or resident in the country for two years or more.

Population figures were obtained from estimates for 1985[2] which take account of projections from the 1981 census, the 1977–8 national dwelling and housing survey, and the 1981 labourforce survey. The proportion of the population aged 0–14 years was estimated as 34% of people originating from the Indian subcontinent, 26% from the other ethnic groups, and 18% of the white population, based on local 1981 census figures and a previous national study.[1] The urban priority area (total population 200 000) includes the inner city and most of the poorer housing estates. It contains 60% of supplementary benefit claimants, 60% of the unemployed, 75% of the ethnic minority population, but only 28% of the total city population

Results

A total of 38 active cases and 35 children who were given chemoprophylaxis against tuberculosis were studied. The demographic characteristics of children included in the study are summarised in table 1. The numbers of active and chemoprophylaxis cases

Table 1 *Demographic characteristics of children (excluding recently arrived immigrants) with active tuberculosis or receiving antituberculous chemoprophylaxis in Leeds 1982–6*

	No of children	*Sex M/F*	*Age (%) in years*			*Ethnic origin*			
			0–4	*5–9*	*10–14*	*White*	*Indian subcontinent*	*Afro-Caribbean*	*Vietnamese*
Active tuberculosis	38	18/20	15 (40)	13 (34)	10 (26)	33	2	2	1
Chemoprophylaxis	35	21/14	14 (40)	10 (29)	11 (31)	31	4	—	—

Table 2 *Number of cases of childhood tuberculosis, child population (aged 0–14 years), and mean annual rates by place of residence and ethnic origin in Leeds 1982–6. Figures in bold type refer to active cases, others to children receiving chemoprophylaxis*

	Place of residence		*Totals*	*Annual rate per 100 000*
	Urban priority area	*Non-urban priority area*		
Ethnic group				
Indian subcontinent	**1/4900**	**1/1600**	**2/6500**	**6·2**
	4/4900	0/1600	4/6500	12·3
Other non-white*	**3/3600**	**0/1300**	**3/4900**	**12·2**
	0/3600	0/1300	0/4900	0
White	**16/31 500**	**17/89 600**	**33/121 100**	**5·5**
	20/31 500	11/89 600	31/121 100	5·1
Totals	**20/40 000**	**18/92 500**	**38/132 500**	
	24/40 000	11/92 500	35/132 500	
Annual rate per 100 000	**10·0**	**3·9**	**5·7**	
	12·0	2·4	5·3	

*Two Afro-Caribbean, one Vietnamese

classified by ethnic group and place of residence, child population estimates, and calculated annual rates for tuberculosis are shown in table 2. Children with active disease whose families originated from the Indian subcontinent had a similar rate (6·2) compared with white children (5·5 per 100 000). Children living in the urban priority area had a rate 2·6 times higher than those living elsewhere in the city (10 compared with 3·9 per 100 000).

Twenty three (60%) of the active cases presented to the chest clinic as contacts of known cases of tuberculosis. Twenty of these contacts had asymptomatic primary lung infections, two had a slight cough, and one had a pleural effusion. Of the remaining 15 active cases, one was referred to the chest clinic because of symptoms suggestive of tuberculosis and one presented to a paediatric clinic with erythema nodosum. The other 13 cases were diagnosed after admission to a paediatric ward: six had pulmonary disease, three had tuberculous lymph nodes, one had both pulmonary and cervical node disease, one had miliary spread and tuberculous meningitis, one had Pott's disease, and one had tuberculous peritonitis.

None of the 21 children with primary complexes and only one of the three children with tuberculous lymph nodes were from ethnic minorities. Of the 11 children with more advanced disease, four (three pulmonary and one Pott's disease) were from ethnic minorities.

None of the active cases had received BCG immunisation. Twenty seven had been Heaf tested before diagnosis Nineteen had a response of grade three or more, and of the eight with a grade two response, six were under 5 years of age. Nine children had been Mantoux tested and all showed a positive response except for a one year old with miliary disease who showed a negative response to 1 in 1000 tuberculin. In two children there was no record of a tuberculin test, one had positive sputum microscopy, and the other had typical lymph node histology

Five of the children receiving chemoprophylaxis had been immunised with BCG, two were infants, and the other three were aged 10, 12, and 13 years. Both infants were not Heaf tested, their mothers had sputum positive pulmonary tuberculosis. The remaining 33 children receiving chemoprophylaxis all had a Heaf test result of grade two or more.

Discussion

Leeds chest clinic provides a diagnostic and therapeutic service for contacts, new immigrants, and those with suspected or proven tuberculosis. Asian infants and those with a family history of tuberculosis are referred by their health visitors to the chest clinic for BCG immunisation by the age of 8 weeks. The uptake of this service is 86%. BCG immunisation is offered in school to all Heaf negative children aged 13 years In 1986, 12% of Leeds 13 year olds had positive Heaf tests, 81% received BCG, and 7% did not (P Ainsworth, personal communication).

Since January 1982, children receiving antituberculous chemoprophylaxis have not been notified and have been recorded separately from those with active tuberculosis. We have studied all active cases and all those receiving chemoprophylaxis for the subsequent five years after excluding recently arrived immigrants. Two important conclusions emerge.

First, although the total number of active cases was small, none had been immunised with BCG. Second, there were very few children from ethnic minorities with active disease and the rate for children whose families originated from the Indian subcontinent was similar to that for white children (table 2). The rate for Asian children is considerably lower than those reported in the 1983 national survey[1] and this is likely to be due partly to a decrease in the numbers of new immigrants, partly to the improved living standards of some Asian communities, but also to the protective effect of BCG immunisation of Asian infants. Neonatal BCG immunisation has been shown to give children an estimated protection against tuberculosis of between 64%[3] and 75%.[4]

The results of this study require confirmation from other urban centres, whose ethnic minority communities may have different socioeconomic characteristics. In Blackburn for example, 89% of notified childhood tuberculosis was among Asians.[5] One possible source of bias in our study was that ethnic minority children may have been under-represented in the detected cases of tuberculosis due to less good use of the health services. Some support for this possibility is provided by the fact that four of the 11 more advanced cases came from an ethnic minority, but the numbers are too small to make definite conclusions.

Poverty, as shown by residence within a designated urban priority area, was a better indicator than ethnic group of the risk of tuberculosis (table 2). Selection of infants for BCG immunisation by ethnic group or by family history, while ensuring adequate protection for the immunised, has resulted in a small number of cases occurring in unimmunised children, usually from poorer sections of the city. Any form of selective policy has its problems. It may be wiser to immunise all babies on the postnatal wards, as is the practice in some hospitals,[4] particularly because of the expected increase in the prevalence of adult tuberculosis associated with AIDS.[6]

We thank the clinicians involved for permission to study children under their care

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Transient intracranial hypertension of infancy

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SUMMARY Four infants were seen on six separate occasions with febrile illnesses associated with a bulging anterior fontanelle and irritability. They had signs of a transient form of intracranial hypertension.

The irritable infant who presents with a bulging fontanelle and fever may have meningitis. We have recently seen four infants because of a bulging fontanelle and irritability, associated with poor feeding and fever. None of them had otitis media, meningitis, or an intracranial space occupying lesion and their signs settled within a few days.

CASE 1

A previously healthy 8 month old girl presented with a 24 hour history of vomiting and fretfulness. Examination showed an irritable, febrile infant with a head circumferance of 46·0 cm (75th centile), diastasis of cranial sutures, and a bulging anterior fontanelle. There was no otitis media or focal signs of infection.

A computed tomogram showed mild communicating hydrocephalus, and lumbar puncture showed a raised opening pressure of 40 cm cerebrospinal fluid. She improved rapidly after lumbar puncture and was discharged home after 48 hours. Four days later she was readmitted with similar physical signs and a repeat computed tomogram was identical to the first one. Daily lumbar punctures were started and her symptoms resolved in two days.

CASE 2

A 5 month old boy was admitted to hospital with a three day history of fever, irritability, and vomiting His parents had noticed his anterior fontanelle bulging for 24 hours. He had been born at 33 weeks' gestation and had had no neonatal problems. The head circumference at birth was on the 50th centile and his head growth was normal up to 3 months of age.

Examination showed an alert, mildly feverish infant whose head circumference was 45·0 cm (97th centile). The fontanelle was tense and bulging, nevertheless there was no suture separation. A cerebral ultrasound scan was normal.

He settled over two days and was discharged home, but readmitted three weeks later with a bulging fontanelle. His head circumference had increased to 46·1 cm. Because of concern about a possible space occupying lesion a computed tomogram was performed, which showed mild communicating hydrocephalus. His signs of raised intracranial pressure settled spontaneously over three days.

CASE 3

A 6 month old boy presented with a 12 hour history of fever and bulging of his fontanelle, both of which had been noticed by his parents. He had been born at term and had had birth asphyxia requiring intubation for seven minutes but he had made an uneventful recovery. Follow up over the next three months showed normal growth and development.

His temperature was 38·8°C and he was irritable on handling with episodes of screaming. His fontanelle was tense and bulging and his head circumference was 43·0 cm (25th centile). There were no focal signs of infection. Examination of his cerebrospinal fluid and a cerebral ultrasound scan were normal.

His fontanelle slackened promptly after lumbar puncture and his irritability rapidly resolved He was discharged three days later.

CASE 4

A previously healthy 7 month old boy presented with an acute illness of eight hours duration, during which he had been screaming and was reluctant to feed. He was found to be slightly irritable and had a temperature of 37·5°C. His anterior fontanelle was bulging at rest. The head circumference was on the 97th centile. A cranial ultrasound scan was normal. Because his general condition improved and there was concern about raised intracranial pressure an initial lumbar puncture was temporarily deferred. His fever and symptoms settled somewhat on treatment with regular paracetamol. Two days after admission he developed a left upper lobar pneumonia which responded to antibiotics; three days later his fontanelle was normotensive.

Discussion

These infants had six episodes of acutely raised intracranial pressure without evidence of central nervous system infection or a space occupying lesion. All had negative cerebrospinal fluid, blood, and urine cultures and normal plasma electrolyte and calcium concentrations. No specific cause could be found for the raised intracranial pressure but all episodes were associated with a febrile illness, in one case a chest infection. Two of the four cases had normal sized ventricles on cranial ultrasound scan and these are similar to benign intracranial hypertension.[1] The two other infants had enlarged ventricles and widened subarachnoid spaces on a computed tomogram· features of a mild communicating hydrocephalus Follow up of all four children for several months showed normal developmental progress and normal head growth.

We suggest that a non-specific infective illness has interfered with absorption of the cerebrospinal fluid from the arachnoid villi. The widened cerebrospinal fluid spaces in two cases support this hypothesis. Benign intracranial hypertension has previously been described in children during roseola infantum,[2] upper respiratory tract infections,[1] and otitis media.[3] Other conditions causing benign intracranial hypertension were excluded.[4–6]

The first three infants had rapid resolution of their symptoms after lumbar puncture. This procedure reduces intracranial pressure, an effect which may last for up to a day if cerebrospinal fluid continues to leak from the dural puncture site.

We wish to add a note of caution. The infant with signs suggestive of meningitis but who has a normal lumbar puncture may have transient intracranial hypertension. If there is no clinical improvement, however, the possibility of early meningitis that has failed to cause an initial pleocytosis must be considered—antibiotics should be commenced and the lumbar puncture repeated.

This group of infants developed a transient rise in intracranial pressure without evidence of central nervous system infection Discussion with colleagues leads us to believe that this condition is much more common than has previously been recognised

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Cerebral systemic lupus erythematosus

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SUMMARY Cerebral systemic lupus erythematosus is uncommon in childhood. Three further cases are presented to draw attention to the unusual and varied clinical manifestations of this condition.

The diagnosis of cerebral systemic lupus erythematosus (SLE), even in adults, is easily overlooked in the absence of more widespread systemic involvement by the disease. In children there is an even greater likelihood of misdiagnosis because of the rarity of the disorder in this age group.[1] The present report of three children who presented with cerebral manifestations of SLE emphasises not only the varied features of such neurological involvement but also the need to investigate any obscure neurological illness in children by immunological tests.

Case reports

Case 1 A boy aged 6 years presented with writhing movements of the left arm followed several weeks later by sudden flexion and extension movements of the left leg. These worsened over the next three months and were accompanied by the evolution of dystonia of the left eyelid and episodic deviation of the eyes to the left. Six months later he developed focal tonic clonic seizures affecting the left side which were difficult to control, despite the use of phenytoin, sodium valproate, clonazepam, and phenobarbitone. Over the next two years he followed a fluctuating course, with variation in his dystonia and mobility. Attention span, behaviour, and both reading and writing all deteriorated. Investigations, including biochemical screening of plasma and urine for inherited or acquired metabolic disorders, a computed tomogram of the brain and nuclear magnetic resonance brain scan, carotid angiography, and brain biopsy all failed to give a diagnosis. An area of atrophy in the head of the left caudate nucleus was the only finding of note. At the age of 9 years he developed a 'lupus syndrome' characterised by arthralgia, lymphadenopathy, and a morbilliform rash, which was initially thought to due to his anticonvulsant treatment. The presence of changes pathognomonic for SLE on immunohistology of a skin biopsy specimen, together with the presence of characteristically high titre antibodies to double stranded DNA (table), however, suggested that the whole illness, including the presenting neurological features, was the result of SLE Treatment with prednisolone (40 mg/1·73 m^2/day) was introduced with a dramatic improvement not only in the lupus syndrome but also in behaviour and intellectual function. Gradual withdrawal of the prednisolone over a period of a month was followed by a deterioration which, however, responded once more to the reintroduction of steroids and a small supplement of azathioprine. These measures were followed by an appreciable improvement in behaviour, speech, and in school performance. Control

Table *Investigational and immunological findings in three children with neurological manifestations of systemic lupus erythematosus*

	Case 1	*Case 2*	*Case 3*
Erythrocyte sedimentation rate (mm in the first hour)	16	81	4
Total leucocyte count ($\times 10^9$/l)	5·0	8·8	8·2
Total lymphocyte count ($\times 10^9$/l)	1·2	1·94	3·69
Antinuclear antibody (reciprocal of titre)	500	300	100
Antidouble stranded DNA antibody (reciprocal of titre)	640	160	Negative
Antilymphocyte antibody	Positive	Positive	Negative
C3 (g/l)*	0·86	1·73	0·80
C4 (g/l)†	0·10	0·38	0·28
Urea (mmol/l)	3·2	0·5	5·7
Skin biopsy specimen immunohistology	Granular deposits of IgG/IgM at dermoepidermal junction	Granular deposits of IgG/C3 at dermoepidermal junction	Vasculitis with IgM/C3 in dermal vessels and deposits of C3 at dermoepidermal junction

*Reference range 0·20–0·65 g/l, †reference range 0·15–0·45 g/l

of the epilepsy has remained variable on continuing anticonvulsant treatment and there has been no improvement in the dystonia, despite the performance of stereotactic surgery.

Case 2. A 6 year old girl developed headaches and blurred vision, which resolved spontaneously over a five week period. A computed tomogram of the brain and a cerebral angiogram were both normal. Two months later she developed fever and meningism with a pleocytosis in the cerebrospinal fluid (270 leucocytes$\times 10^6$/l; 75% polymorphonuclear leucocytes). Bacteriological studies, however, gave negative results and she failed to respond to antimicrobial chemotherapy. Her illness progressed with the development of ptosis, nystagmus, intention tremor, a left VII nerve palsy, and bilateral extensor plantar responses. Recent experience with case 1 prompted further immunological investigations (table), which suggested a diagnosis of cerebral SLE on the basis of high titre antinuclear antibodies coupled, once more, with pathognomonic changes on immunohistology of a skin biopsy specimen. She made a dramatic response to high dosage prednisolone (60 mg/1·73 m^2/day) with resolution of fever and all neurological signs and has continued to make excellent progress physically and educationally on a gradually reducing alternate day regime of prednisolone. It proved possible to wean her off steroids after some 12 months' treatment with no evidence, as yet, of any relapse.

Case 3. A 7 year old girl presented with a one week history of ocular flutter and intention tremor. A computed tomogram of the brain was normal and a diagnosis of cerebral SLE was again established by immunological screening (table) which, again, showed the presence of high titre antinuclear antibodies and vasculitic changes in immunohistology of a skin biopsy specimen. Her symptoms disappeared after 10 days treatment with high dosage prednisolone (60 mg/1·73 m^2/day) while further progress has been satisfactory on a continuing low dose alternate day regime of prednisolone.

Discussion

SLE is an uncommon disease in childhood with a very variable incidence of involvement of the central nervous system, which ranges from 20% to 44% in two recently published series.[1 2] The most often observed manifestations include seizures, cranial nerve palsies, ataxia, nystagmus, papilloedema, meningitis, tremor, cortical blindness, and coma.[2 3] Neuropsychiatric manifestations including psychosis and personality disorder may also occur. In the present report, the child with hemidystonia is, we believe, the first described case of this syndrome occurring as a result of cerebral SLE. In the series of Yancey *et al* involvement of the central nervous system occurred at the onset of the disorder in 13 of the 16 cases with neurological disease,[2] and this tendency for the central nervous system involvement to be an early feature is evident in the present small group as well

Our cases also show clearly the value of early immunological investigations in children with obscure neurological manifestations. All three children had high titre antinuclear antibodies associated with characteristic changes on immunohistology of skin biopsy specimens, which proved particularly valuable in confirming the diagnosis in the two patients who did not have any other systemic features of the disease.

The high titre antibody to double stranded DNA in case 1 was also helpful in excluding a drug induced lupus syndrome while additional screening for both precipitating antibodies to extractable nuclear antigens[4 5] (such as anti-RNP, anti-Ro, anti-La and anti-Sm) and anticardiolipin antibodies might also have been useful. These additional autoantibodies can help to define subsets of the disease (such as the thrombotic tendency associated with anticardiolipin antibodies[6]) as well as occasionally being positive when conventional testing for antinuclear antibodies produces negative results.

The improved survival reported in recent series of cerebral SLE has been attributed to earlier diagnosis, more aggressive treatment, and appropriate follow up as well as to the recognition of milder cases.[1 2] In our series although the diagnosis in the first case was delayed for three years, increasing awareness and early immunological screening led to a prompt diagnosis in the other two cases who responded well to vigorous steroid treatment and were left without any residual neurological deficit.

We present these cases to show the varied neurological presentations of cerebral lupus erythematosus and to draw further attention to this condition in childhood. In view of its rarity, we feel it would be useful to set up a national register of cases to monitor progress and treatment of the disorder.

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Copper in urine and hair in Indian childhood cirrhosis

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SUMMARY In advanced Indian childhood cirrhosis (ICC) urine copper concentration was higher (range 416–103 448 mg/g creatinine) than in other hepatic diseases (range 67–10 303 mg/g creatinine). In early ICC urine copper concentration was more modestly raised (1188–9470 mg/g creatinine), but rose to high values (2222–42 819 mg/g creatinine) after a single dose of penicillamine 20 mg/kg. A post penicillamine urinary copper creatinine ratio >10 000 mg/g supports a diagnosis of ICC. The concentration of copper in the hair, while increased in advanced ICC, is of no diagnostic value in early cases.

The clinical diagnosis of Indian childhood cirrhosis (ICC) is easy in the late presenting case but is unreliable at an earlier stage. Liver biopsy is therefore necessary.[1] We sought a robust non-invasive diagnostic method and we have therefore evaluated copper concentrations in urine and hair. To obviate the need for 24 hour urine collections, which would not be feasible if the method was to become of value in the field, the copper:creatinine ratio was measured in random samples of urine. The cupriuretic effect of a single dose of penicillamine is of diagnostic value in Wilson's disease,[2] and was studied in ICC and other hepatic disorders.

Hair is painless to collect, easy to store and transport, and provides a historical measure of intracellular copper. Despite well described limitations of hair trace metal analysis,[3] previous workers have suggested that copper concentration in hair is raised in ICC.[4 5]

Methods

Urine was collected from 57 children with ICC and from 21 children with other hepatic disorders (table) in Pune [1] The children studied were part of a prospective review of liver disease, diagnosis being confirmed by a liver biopsy specimen in each case Urine was stored at 4°C in plastic containers and transported in batches to Leicester.

Eight children (aged 4 to 48 months) with early ICC—that is, without jaundice or ascites—and 15 children (aged 3 to 48 months) with other hepatic disorders (table) had urine collected before and 24 hours after an oral dose of penicillamine 20 mg/kg body weight.

Urine, with added ammonium nitrate to give a final concentration of 5% to cause sodium chloride volatisation, was assayed directly for copper by electrothermal atomic absorption spectrophotometry (Pye Unicam SP9).

Containers were shown to be copper free by assaying acid washings. The extent to which containers took up copper from samples (n=10) was found to be insignificant at 0·5 (SD 0·37)%. Repeated assay of an aliquotted urine over a three year period showed good reproducibility (7·32 (0·95) µmol/l urine). Urinary creatinine concentration was determined colorimetrically.[6]

Hepatic copper concentrations in percutaneous biopsy specimens were assayed as previously described [1]

Hair was taken from 40 cases of ICC (age 2–48 months); 18 Pune patients with non-hepatic disorders (age 10–48 months); and 15 Leicester inpatients (age 1–48 months). Snippings were taken from the crown and the entire length assayed. To remove surface contamination samples were washed with 4 ml acetone followed by 4 ml deionised water and then the washings repeated, each wash took 10 minutes Samples were dried, weighed, and then digested in 2 ml of 50% nitric acid at 80°C for three hours. After evaporation to dryness samples were redissolved in 2 ml of 0·1% nitric acid Copper was assayed as above.

A sample of hair repeatedly assayed gave results of 22·6 (9·1) µg copper/g hair.

Clinical, laboratory, and histological variables were recorded as previously described.[1] Values for copper·creatinine ratio showed a skewed distribution and were log transformed for analysis. Groups were compared using Student's unpaired *t* test.

Results

The urinary copper:creatinine ratio in 57 children with ICC was significantly greater than that found in 21 children with other hepatic disorders despite the wide scatter results (p<0·001). Among children with ICC, more advanced disease was associated with higher copper:creatinine values. Ascites and jaundice are late features of ICC, and cases with neither jaundice nor ascites (n=15) had a copper:creatinine ratio with a significantly lower range (416–39 600,

Table *Mean (SD) hepatic copper concentration and urinary copper.creatinine ratio in 57 children (11 girls, 46 boys) with ICC and in 21 children with other hepatic disorders. Urinary copper·creatinine ratio was also assayed in eight children with early ICC and in 15 children with other hepatic disorders before and 24 hours after a single dose of penicillamine 20 mg/kg*

	No of children	*Hepatic copper (µg/g dry weight)*	*Urinary copper creatinine ratio (mg copper/g creatinine)*		
			Median	*Range*	*Log₁₀*
ICC	57	1667 (694)	6781	416–103 448	3 92 (0 52)†
Other hepatic disorders	21	383 (373)	452	67–10 303	2 72 (0 58)†
Chronic active hepatitis	6	498 (309)	282	75–10 303	2·70 (0 73)
Chronic persistent hepatitis	5	162 (42 8)	245	67–3025	2·65 (0 70)
Wilson's disease	1	853			3·0
Cryptogenic cirrhosis	1	1250			3 0
Others*	8	219 (313)	681	77–2000	2·73 (0 54)
		Penicillamine trial			
ICC					
Before	8	1342 (1037)	4311	1188–9470	3 65 (0 30)‡
24 Hours after			28 243	2222–42 819	4 23 (0 52)§
Other hepatic disorders					
Before	15	453 (378)	288	67–10 303	2 74 (0·60)‡
24 Hours after			4115	369–33 333	3 50 (0 60)§

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*Other disorders extrahepatic biliary artresia (n=2), infective hepatitis (n=2), glycogen storage disease (n=1), tuberculosis (n=1), syphilitic hepatitis (n=1), and minor changes (n=1)

†p<0 001, ‡p<0 006, §p<0 001

$\log_{10}$ 3·7 (0·5) than those with both jaundice and ascites (1543–91 707, $\log_{10}$ 4·1 (0·5)) ($p<0·011$). No correlation existed, however, between the copper:creatinine ratio and serum total or conjugated bilirubin, serum transaminases, or hepatic copper.

In early ICC urine copper concentrations were more modestly raised and showed overlap with those found in other liver disorders even though mean values were significantly different (table).

After a single oral dose of penicillamine 20 mg/kg a large rise in urinary copper occurred in children with ICC to values exceeding 10 000 mg/g in seven of eight children. A considerably smaller rise occurred in other hepatic disorders, the post-penicillamine value exceeding 10 000 mg/g in only two children. One of these had Wilson's disease and one had chronic active hepatitis (hepatic copper concentrations being 853 and 508 µg copper/g dry weight respectively, normal <100 µg/g).

Concentrations of copper in the hair of children with ICC (71·9 (55·9), range 13–220) was higher than in the controls from either the United Kingdom (25·8 (14·6), range 11–69) or India (58·7 (39·7), range 16–170) but the wide scatter of results made these differences non-significant. Children with ICC that was clinically judged to be early had a significantly lower hair copper concentration (19·0 (4·3)) than later (92·1 (86·0)) or terminal cases (93·0 (53·0)). There was no correlation between hepatic and hair copper.

Discussion

The present data show that the hepatic copper storage characteristic of ICC is accompanied by greatly raised urine copper:creatinine ratios. In advanced cases values of 10 000–93 030 mg/g were found. Absolute concentrations of copper in the urine were 20·5–856·3 µmol/l, concentrations readily detectable by standard chemical assays. Random urine copper is therefore of some diagnostic value, particularly when coagulation defects make liver biopsy hazardous.

It is, however, in the early case that non-invasive diagnostic methods are more urgently required. The present study shows that in ICC that has not progressed to the development of ascites or jaundice urinary copper:creatinine ratios are modestly raised and do not provide a clear distinction from other hepatic disorders. After a single dose of penicillamine 20 mg/kg, however the ratio sharply increased. Values exceeded 10 000 mg copper/g creatinine in seven out of eight cases. Other disorders associated with raised hepatic copper show a modest post-penicillamine cupriuresis. The other important cause of raised urine copper in infancy, extrahepatic biliary atresia, is clinically quite distinct from ICC, however, while Wilson's disease is rarely symptomatic before 5 years of age, and may be differentiated from ICC by serum caeruloplasmin assay.

Hair copper concentrations are raised in advanced ICC confirming previous reports,[4] [5] but the diagnostic value of this is limited because of the variation in normal values. Exogenous copper contamination contributes to this variation despite meticulous sample preparation.[7] The difference between the controls in the United Kingdom and India may reflect different use of oily scalp preparations or may genuinely reflect copper status. Another disadvantage is that hair copper concentration is normal in the early case in which diagnosis is most difficult.

We conclude that random urine and hair copper concentrations are raised in advanced ICC. While hair copper is of no diagnostic value in early ICC a post-penicillamine urine copper:creatinine ratio greater than 10 000 mg/g is highly suggestive of the diagnosis.

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Blood lead, ethnic origin, and lead exposure

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SUMMARY A survey of blood lead concentrations is reported in a group of 199 young Walsall children (3–6 years of age). The geometric mean blood lead concentration was 0·47 μmol/l (range 0·2–1·6 μmol/l). There were no significant differences in blood lead concentrations between groups of children with different ages, sex, ethnic origin, or environment.

Environmental lead pollution is widely regarded as a risk to child health. Raised blood lead concentrations in children, however, can be due to many causes including airborne lead, lead in soil, lead in household dust, pica, finger sucking, lead in food and water supplies, and lead in oriental cosmetics (for example, surma).

Walsall is an industrial borough with established atmospheric and soil lead pollution. Earlier surveys carried out in Birmingham reported that many inner city children (particularly of the ethnic Asian minority) had raised blood lead concentrations (>1·69 μmol/l).[1 2] The main objective of the present collaborative study was to carry out a pilot survey of blood lead concentrations in young Walsall children and to assess factors that might be expected to influence blood lead concentrations—for example, age, sex, ethnic origin, location of home, diet, and social background.

Subjects and methods

The study population comprised 199 children randomly selected from the Walsall Child Health Register stratified by age, sex, ethnic state, and area of residence. Children aged 3–6 years were from three 'lead polluted' areas and one 'control' area of Walsall (table). A questionnaire covering relevant social and environmental information was completed by a health visitor in the home, along with a hand wipe test for lead A clinical examination for growth parameters and for signs of lead intoxication was carried out together with a venepuncture for blood lead, haemoglobin, and zinc protoporphyrin concentrations.

Blood lead concentrations were measured by atomic absorption spectrometry (Delves' cup). Particular attention was paid to ensuring good accuracy and precision.[3] Measurement of hand lead was carried out with lead free moist tissues used for personal cleansing. Two other tests were selected as potential markers of chronic lead exposure—blood haemoglobin and erythrocyte zinc protoporphyrin.

Results

The frequency distribution of blood lead concentrations for the whole population (figure) shows a distinct positive 'skew', consistent with a log-normal distribution. The geometric mean was 0·47 μmol/l, with extreme values of 0·2 and 1·6 μmol/l. There were no significant differences in blood lead concentrations for children living in the four geographic areas (table). Moreover, age, sex, and ethnic origin did not significantly influence blood lead concentrations. Only five children from the ethnic minority used surma eye make up and this factor did not significantly influence blood lead concentrations.

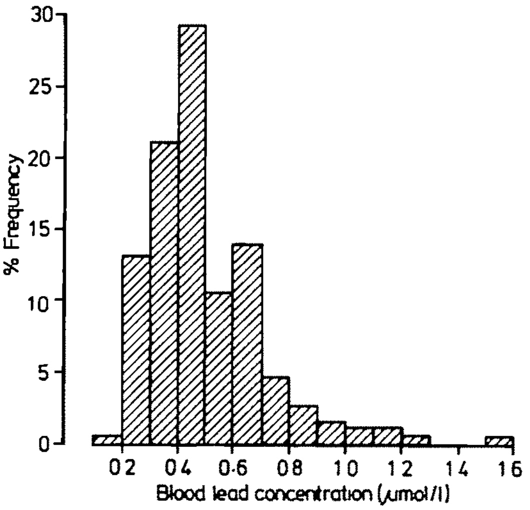

Figure *Histogram of the percentage frequency distribution of blood lead concentrations in Walsall children (n=199) Each interval corresponds to 0·1 μmol/l*

Table *Characteristics of sample population and geometric mean value for blood lead, haemoglobin, zinc protoporphyrin, and hand lead for children living in different locations*

Location	*Sex*	*No of children*			*Blood concentrations (geometric mean)*			*Concentration of hand lead (geometric mean) (µg)*
		White	*Ethnic minority*	*Total*	*Lead (µmol/l)*	*Haemoglobin (g/l)*	*Erythrocyte zinc protoporphyrin (mg/l)*	
Area 1 (High air and soil lead)	M	10	15	25	0·45	119	0·29	5·8
	F	12	13	25				
Area 2 (High air lead)	M	10	9	19	0·48	116	0·26	7·6*
	F	17	13	30				
Area 3 (High soil lead	M	15	—	15	0·43	127	0·26	4·5*
	F	12	—	12				
Area 4 (control area low air and soil lead)	M	21	16	37	0·49	120	0·29	5·3
	F	19	17	36				
Total (range)	M	56	40	96	0·47 (0·2–1·6)	125 (80–170)	0·28 (0·13–1·8)	6·1 (2–198)
	F	60	43	103				

*Significant (p<0·05) difference in hand lead concentrations in these two areas

Hand wipe measurements as a marker for lead exposure were carried out in 194 children. Hand wipe lead in white children was significantly higher (t=2·35, p<0·05) compared with the ethnic minority group.

Measurement of erythrocyte zinc protoporphyrin in 199 children showed no correlation with blood lead concentrations (r=0·02). Moreover, there were no significant differences in erythrocyte zinc protoporphyrin concentrations in children from the four study areas (table). The only positive finding was an association between raised erythrocyte zinc protoporphyrin concentrations and significant iron deficiency anaemia.

The geometric mean blood haemoglobin concentration was 125 g/l, with extreme values of 80 and 170 g/l. Eighteen children (9%) had haemoglobin concentrations less than 110 g/l and were regarded as being anaemic. There was no significant correlation between haemoglobin and blood lead concentrations (r=0·10). There were also no significant differences in mean haemoglobin concentrations for children living in the four study areas (table). There was, however, a highly significant negative correlation (r=−0·65, p<0·01) between blood haemoglobin and erythrocyte zinc protoporphyrin concentrations. The plasma ferritin concentrations in children with anaemia were all less than 10 µg/l (normal range 15–140 µg/l). No children were found with either haemoglobinopathy or parasitic infection.

Clinical examination of all the children did not show any symptomatology suggestive of lead toxicity. There was no history of pica in any child. The height-weight statistics of the white children in the study fell within the expected range for European children. Although some children from the ethnic minority group were, as expected, below the third centile for both weight and height, there was no evidence of growth pathology.

Discussion

The main finding of this survey of blood lead concentrations in stratified populations of Walsall children was that the actual concentrations were surprisingly low. Moreover there were no significant differences in mean blood lead concentrations for groups of children of different age, sex, ethnic origin, or area of residence. Hand lead measurements were unhelpful in identifying children with relatively high blood lead concentrations. The present findings, therefore, are consistent with some recent and well conducted studies of blood lead concentrations in children living in other parts of the United Kingdom[4 5] and well within current European Economic Community and Department of Health and Social Security guidelines, but they are at variance with earlier surveys carried out on preschool children in Birmingham.[1 2] The present findings for concentrations of erythrocyte zinc protoporphyrin question the usefulness of this assay as a screening test for lead exposure.

The principal conclusion is that blood lead concentrations in Walsall children are relatively 'low', even in children living in relatively 'polluted' areas. If the values are representative of the population at large, they reflect very little risk to the health of children in Walsall. From the clinical examinations carried out on the children, there were no obvious physical or behavioural problems that could be related to lead exposure. The possibility of there being subtle deleterious effects of 'low level' lead exposure on child behaviour or intelligence could not be ruled out by the present study, but these effects, if real, are tiny compared with other factors which influence childrens' physical and mental development.[6]

We express our appreciation to the families of Walsall and their general practitioners, who allowed us to study the children, and to the health visitors based at Walsall Manor Hospital who carried out the field work for the survey We also thank staff of the department of clinical chemistry, Walsall Manor Hospital and the department of haematology, Dudley Road Hospital, Birmingham for carrying out additional investigations

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Sublingual nifedipine in acute severe hypertension

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SUMMARY Sublingual nifedipine was used for the treatment of acute severe hypertension in 12 children with renal disease. An average dose of 0·24 mg/kg was safe and proved effective on most occasions within 30 minutes with a median duration of action of three hours. There were no major adverse effects.

The current recommendations for the treatment of hypertensive crises in children advocate the use of intravenous infusions of labetalol or sodium nitroprusside.[1] Administration of these drugs has the disadvantage that they require parenteral administration and nitroprusside has to be protected from light to prevent decomposition. A drug that could be given orally that would act rapidly but would not cause profound hypotension would be an advantage. Nifedipine administered sublingually has been shown to be a safe and effective means of lowering blood pressure in adults.[2 3] Its advantages are the ease of administration, absence of serious side effects, and the fact that it has been shown to increase cerebral blood flow thus reducing the risk of cerebral ischaemia.[2]

Over an 18 month period from February 1986 we have collected data on the use of nifedipine on 35 occasions in 12 children with severe hypertension.

Patients and methods

The 12 children with known renal disorders were all studied while inpatients (table 1). Their ages ranged from 6–15 years and weights from 16–60 kg. Eleven of the children were being treated with other antihypertensive drugs Each child had an acute rise in blood pressure recorded on at least two occasions before treatment and needed urgent treatment In each case the diastolic blood pressure was equal to or greater than 110 mm Hg. Children with features of hypertensive encephalopathy were not studied. Children below 30 kg body weight were given 5 mg nifedipine and children weighing 30 kg or more 10 mg. The dose range was 0·18 to 0·32 mg/kg with a mean dose of 0·24 mg/kg. The capsule was administered either by being cracked between the teeth and held under the tongue or by initially piercing the capsule with a needle and squeezing the contents out under the tongue. The blood pressure and pulse were measured before treatment, at 15 and 30 minutes, and then hourly for six hours. The blood pressure was measured with the child lying down by either one observer using a sphygmomanometer and an appropriate sized cuff covering at least two thirds of the upper arm, or an automated oscillometric device (Dinamap) when more than one observer monitored the blood pressure.

During the study period all other antihypertensive drugs were withheld for six hours unless the diastolic blood pressure remained above 110 mm Hg. We used the following criteria to assess whether sublingual nifedipine was effective: a fall in the mean arterial pressure of at least 20 mm Hg or the diastolic pressure falling to below 100 mm Hg. The means and 95% and 99% confidence intervals were calculated for the falls in blood pressure observed and the appropriate p value determined using the *t* distribution.

Results

On 35 occasions (12 patients) the effect of sublingual nifedipine was studied over the first 30 minutes after administration. These results are shown in table 2. There was a highly significant fall ($p\leq0·01$) in the systolic, diastolic, and mean blood pressures, the largest fall being observed in the diastolic pressure. Using each of our criteria for effectiveness they were fulfilled on 25 of the 35 occasions (71%). Two children (patients 4 and 10) failed to respond on three separate occasions. This was felt to be due to concurrent hypervolaemia. Two other initial non-responders did respond on other occasions. The magnitude of the pretreatment blood pressure did not influence the size of the response obtained.

On 20 occasions (seven patients) the blood pressure was monitored hourly during a six hour period after the administration of nifedipine. The changes in the mean systolic and diastolic pressures are shown in the figure. On 17 occasions (six patients) the diastolic blood pressure fell below 100 mm Hg, and remained below this value from 30 minutes up to six hours (median duration of three hours). A variable duration of response was seen in those children who received the drug on more than one occasion. In those patients in whom nifedipine proved effective the lowest blood pressure was reached within the first hour. The minimum blood pressure recorded was 120/60 mm Hg and the maximum pulse observed was 140 per minute in a child who had a large fall in mean blood pressure of 50 mm Hg and complained of palpitations. Apart from this one occasion in one child, reflex tachycardia was not seen and there was no difference seen in the mean change in pulse rate whether the children were on β blockers or not.

Although nifedipine was well tolerated, most of the children commented on the unpleasant taste.

Table 1 *Clinical details of patients studied*

Patient No	*Age (years)*	*Nifedipine dose (mg/kg)*	*Diagnosis*	*Other drugs taken*
1	10	0·20	Chronic renal failure, CAPD*	Captopril, Nifedipine
2	14	0·27	Renal transplant	Metoprolol, nifedipine, enalapril
3	11	0·26	T cell lymphoma, renal insufficiency	Labetalol
4	14	0·20	Chronic renal failure, CAPD*	Hydrallazine, labetalol, enalapril
5	10	0·18	Renal transplant	Labetalol, nifedipine, hydrallazine
6	14	0·31	Renal transplant	Labetalol, nifedipine
7	14	0·29	Renal artery stenosis	Hydrallazine
8	15	0·22	Renal transplant	Metoprolol, prazosin
9	6	0·32	Chronic renal failure, CAPD*	Hydrallazine
10	12	0·22	Haemolytic uraemic syndrome	None
11	14	0·19	Chronic renal failure	Captopril, nifedipine
12	12	0·24	Reflux nephropathy	Labetalol, hydrallazine

*CAPD=continuous ambulatory peritoneal dialysis

Table 2 *Effect of sublingual nifedipine on blood pressure after 30 minutes*

	Systolic pressure (mm Hg)	*Diastolic pressure (mm Hg)*	*Mean arterial pressure (mm Hg)*
Mean (SD) pretreatment blood pressure	16– (13·2)	118 (7·6)	133 (7·1)
Mean (SD) blood pressure 30 minutes after treatment	14– (13·7)	89 (13·5)	106 (12·4)
Mean change in blood pressure (95% confidence intervals)	−22·8 (−27·5 to −18·1)	−29·6 (−35·3 to −23·9)	−26·6 (−32·3 to −20·9)

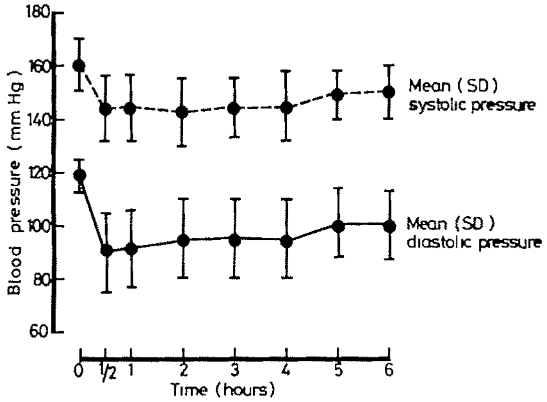

Figure *The effect of sublingual nifedipine on blood pressure over a six hour period (20 occasions in seven patients)*

The only adverse effects were palpitations (two occasions), facial flushing (two occasions), headache (one occasion), and tiredness (one occasion). One patient vomited immediately after being given the drug and did not take part in the study. No patient complained of dizziness; symptomatic hypotension was not seen.

Discussion

The results of our study show that sublingual nifedipine in a mean dose of 0·24 mg/kg is a safe and effective drug that will rapidly lower blood pressure in children with acute severe hypertension. On 10 occasions (three patients), however, it proved not to be effective as judged by our criteria and the median duration of action was only three hours. Other studies in children have shown it to be effective on each occasion and the duration of action to last for six hours.[4-6] These differences could be attributable to the slightly lower dose range in our study of 0·18–0·32 mg/kg as opposed to 0·25–0·5 mg/kg. We encountered no major adverse effects and generally the drug was well tolerated and preferred to an intravenous drug. We consider the drug to be safe and have instructed selected patients to use it at home or on holiday if they have an episode of severe hypertension. We did not use the drug in children below the age of 5 years but it would be possible to use it on younger children by aspirating the contents of a capsule with a syringe and administering the required dose per kg body weight sublingually The volume inside the 10 mg and 5 mg capsules is 0·34 ml and 0·17 ml, respectively (Bayer UK Ltd, personal communication). Precautions should be taken to protect the drug from light as it will degrade rapidly. Although we would not recommend it being used in hypertensive encephalopathy, where we favour the use of a drug which can be titrated such as intravenous labetalol, we believe that sublingual nifedipine has a role in the treatment of acute severe hypertension in children.

Acknowledgements to the nursing staff of ward 15 for their help and cooperation

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Severe failure to thrive and diarrhoea caused by laxative abuse

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SUMMARY We report a case of chronic administration of Epsom salts leading to diarrhoea and severe weight loss in a 7 month old girl.

Failure to thrive in association with loose stools is a frequent diagnostic problem. We report our experience.

Case report

A girl, weighing 2500 g, was born at 41 weeks' gestation to a young single mother. At age 3 months she developed 'pertussis', then presented one month later with poor feeding, lethargy, weight loss, and passage of six to ten loose stools per day. She was admitted to hospital where breast feeding was supplemented with bottle feeds. All investigations gave normal results (sweat test, thyroid function tests, stools for occult blood and microbiology, and blood for routine haematology and biochemistry). The child recovered and was discharged after six days. Two weeks later she developed typical chicken pox and received antibiotics for a 'chest infection'. Although weight increased slowly, her stools remained loose and frequent.

During the next two weeks she was treated by the family practitioner for another chest infection and was also thought to have had rubella.

The health visitor became increasingly concerned about her 'failure to gain weight' and continued watery stools despite the child being alert and feeding well. On readmission, age 0·38 years, she weighed 4190 g (below the 3rd centile). Investigations were performed including repeated stool bacterial and viral culture, stool chromatography, serum lipids, radiography of long bones, serum immunoglobulins and T cell subsets; all gave normal results. In view of her numerous illnesses, a secondary cows' milk protein intolerance was suspected and a change to a soya milk resulted in an immediate but temporary improvement. This pattern of temporary improvement was repeated several times with other empirical feed changes. During three weeks in hospital mother and baby were inseparable, with the mother remaining calm and smiling throughout.

After a weekend at home she was readmitted in a severely dehydrated state, and after resuscitation intravenous feeding was commenced. Intermittent diarrhoea continued but collection of stool samples proved difficult. Eventually stool electrolytes were analysed. A large solute gap existed between measured osmolarity (284 mmol/kg) and measured electrolytes (sodium <5 mmol/l, potassium 15·4 mmol/l, chloride 23 mmol/l). Urine contamination was excluded by a low faecal urea. Sugars including lactulose were absent. Faecal magnesium was 170 mmol/l, which, for her approximately measured daily stool volume, was equivalent to 4·5 mmol/kg/24 hours (about 10 times normal) Urinary magnesium was also high (again 10 times normal) though plasma magnesium remained normal due to high urinary clearance. Confronted with this information the mother admitted to administering Epsom salts so that symptoms were maximised and 'the doctors would take her more seriously'. A box of Epsom salts (58 g), a feeding bottle containing 350 mmol/l of magnesium, and some distilled water were found in her possession. After separation from the mother

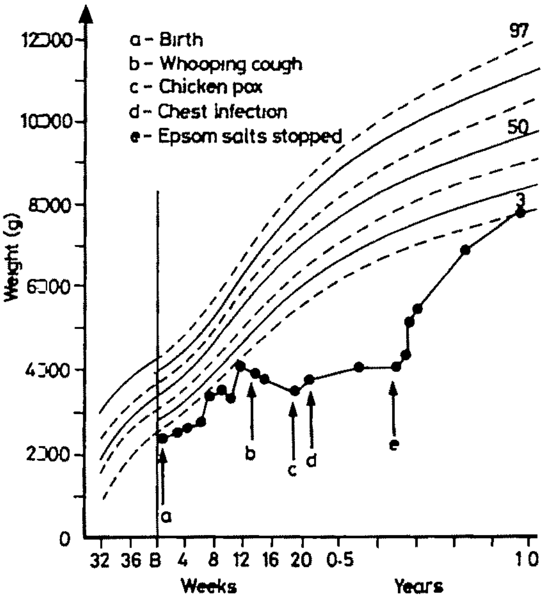

Figure *Poor weight gain in an infant found to have been receiving Epsom salts, and subsequent rapid catch up growth.*

and subsequent fostering the diarrhoea ceased and the child's weight gain was dramatic (figure).

Discussion

The deliberate administration of harmful substances was included in early descriptions of child abuse[1] These substances include both household products and drugs, which were often prescribed for adults in the family.[2] Previous reports have emphasised that a prerequisite for diagnosis is a low threshold of suspicion.[3 4] Disturbances of bowel function with poor weight gain are commonly seen in infants, but reports of deliberate overdosing with dangerous drugs are relatively uncommon, and laxative abuse in very young children is exceedingly rare. These factors, the exemplary behaviour of the parents, and the trust which doctors place in parental histories, militate against early diagnosis with potentially life threatening consequences.

Even when the diagnosis is considered, proving it is often difficult and in this case the stool electrolytes were vital in distinguishing an osmotic from a secretory diarrhoea. The severity of weight loss and the near fatal episode of dehydration emphasises the need to consider pharmacological abuse where the clinical picture is unusual.[2]

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Clostridium difficile in an oncology unit

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SUMMARY In one year 21 new cases of *Clostridium difficile* infection occurred on a paediatric oncology unit. Eleven cases were in a two month period. This infection should be regarded as a communicable disease. Investigations to detect *C difficile* should be carried out in children with malignant disease who have diarrhoea.

Clostridium difficile has been increasingly recognised as an aetiological agent of acute and chronic antibiotic associated diarrhoea and pseudomembranous colitis.[1] There have been reports of outbreaks in hospital units as well as sporadic cases. Patients with malignant disease receiving immunosuppressive treatment are at risk of opportunistic infection. As they also receive numerous courses of antibiotics and have frequent hospital admissions throughout their treatment they are at particular risk of *C difficile* infection.[2 3] In addition cancer chemotherapy may predispose to gut colonisation with *C difficile*[3] We report an outbreak of infection with this organism in a paediatric oncology unit associated with a change in antibiotic policy.

Patients and methods

All patients admitted to the paediatric oncology unit, a 10 bedded ward exclusively for children with cancer, in Newcastle upon Tyne during 1986 who had diarrhoea associated with *C difficile* were included in this study. Diarrhoea was defined as a change from normal bowel pattern with passage of two or more consecutive unformed stools. Stool specimens from patients with diarrhoea were examined for the presence of *C difficile* and its cytotoxin in addition to routine virological and bacteriological investigations.

Specimens were inoculated onto Columbia blood agar containing cycloserine and cefoxitin as selective agents. Detection of cytotoxin was performed by standard laboratory methods.[4]

Since 1981 patients on the unit with neutropenia and fever have received empirically gentamicin and azlocillin. During 1985 only 61% of Gram negative bacilli isolated were sensitive to azlocillin, therefore in March 1986 cefuroxime was substituted for azlocillin.

Because of an apparent increase in the number of patients with *C difficile* infection early in 1986, stool specimens were examined for *C difficile* from all children admitted during the five month period from the middle of May to October 1986. Also the use of cefuroxime was discontinued and azlocillin and gentamicin were instituted.

All patients who were positive for culture or toxin for *C difficile* received an oral course of vancomycin (125 mg orally three times daily) and if the culture or toxin remained positive a further course was given consisting of three days of vancomycin with a three day rest period repeated three times.[5]

Results

During the year 21 patients, nine girls and 12 boys, aged 1–19 years had one or more episodes of diarrhoea associated with *C difficile* during some stage of their treatment (figure). Eleven of these occurred in a two month period. Nineteen had a mild illness but in two the symptoms were more serious with bloody diarrhoea and abdominal pain. All were receiving chemotherapy for either leukaemia (11 patients) or solid tumours (10 patients). At the time of presentation with *C difficile* associated diarrhoea, 10 patients had an absolute neutrophil count less than $1{\cdot}0\times10^9/l$. In 15 patients both the organism and the toxin were present in faeces but in five only the organism and in one only the toxin was detected.

In all 21 patients symptoms resolved with treatment with oral vancomycin and the organism and its toxin could not be detected in stools after treatment. In nine patients (43%), however, *C difficile* or its toxin were detected again at a later date. Such recurrence of colonisation was usually, but not always, associated with symptoms. Some children had multiple recurrence, giving a total of 35 episodes of infection in 21 patients (table).

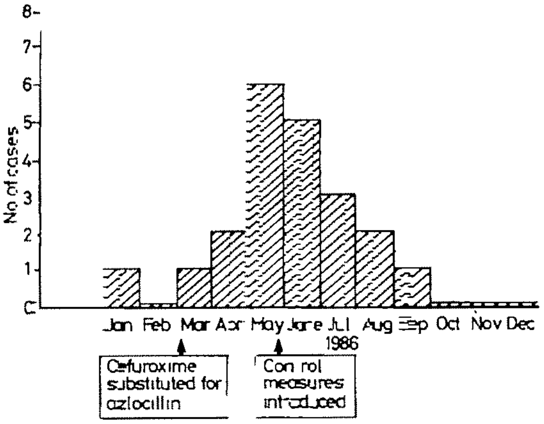

Figure *Number of new cases of Clostridium difficile associated diarrhoea in each month for 1986*

Table *Recurrence of clostridium difficile in the stool of 26 patients*

	Isolation of Clostridium difficile		Diarrhoea	
	No of children	Total No of episodes	Present	Absent
Symptomatic patients				
No of relapses				
0	12	12	12	0
1	5	10	8	2
2	3	9	7	2
3	1	4	4	0
Subtotal	21	35	31	4
Asymptomatic patients				
No of relapses				
0	3	3	0	3
1	2	4	0	4
Subtotal	5	7	0	7
Total	26	42	31	11

During the five month period in which routine screening of all patients admitted to the ward was carried out, 77 patients were admitted on 272 occasions. In addition to the 14 symptomatic patients during this screening period described above, five asymptomatic patients were found to have *C difficile* in their stools. In two of these patients colonisation recurred after treatment (table).

Toxin was detected in 18 out of 31 (58%) episodes of *C difficile* infection associated with diarrhoea but only in two of 11 asymptomatic isolations ($p<0{\cdot}02$). All 10 episodes of *C difficile* infection in patients with an absolute neutrophil count of less than $1{\cdot}0\times10^9/l$ were symptomatic.

Discussion

C difficile has been isolated occasionally in the paediatric oncology unit in Newcastle since 1980. The outbreak described above was associated with a change in antibiotic policy from the use of azlocillin to cefuroxime. Although *C difficile* associated diarrhoea does occur without prior exposure to antibiotics, most cases reported do implicate an association and the cephalosporins appear to be a particular problem.[6]

There are a number of potential causes of diarrhoea in children receiving treatment for malignant disease. In addition to bacterial, viral, and parasitic infection chemotherapy can cause small bowel mucosal damage resulting in diarrhoea. It is important that diarrhoea is not accepted as a normal symptom of cancer chemotherapy and that stool specimens are sent for full bacteriological and viral investigations including examination for the presence of *C difficile* and its toxin. Relapse after the discontinuation of treatment with vancomycin, metronidazole, or bacitracin has been reported with incidences ranging from 5% to 59%.[5] In the present series, the symptomatic relapse rate was 38%

There now seems little doubt that *C difficile* infection is a communicable disease, which may cause outbreaks of infection in hospital [2 3] Patients with diarrhoea known or suspected to be due to *C difficile* should be isolated and 'barrier-nursed' in the same way as patients with other recognised gastrointestinal pathogens. The low incidence of asymptomatic carriage detection in this study suggests that screening is probably not worthwhile as a routine preventive measure except during an outbreak. Antibiotic policies should be reviewed if an outbreak occurs.

It is possible that the outbreak could have been aborted if control measures had been commenced sooner. Recognition that an outbreak is occurring is therefore vital, particularly in units which already have a low 'background' incidence of infection.

Therefore we suggest that paediatric oncology units should monitor the number of cases of *C difficile* infection and if there is any evidence of an increasing incidence control measures should be started.

With early treatment severe life threatening illness may be prevented. The presence of either the toxin or the organism may be related to symptoms, and the absence of the toxin should not dissuade the physician from considering *C difficile* as a pathogen and commencing specific treatment.

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Variation in lower leg growth with alternate day steroid treatment

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SUMMARY Daily growth of the lower leg in a child receiving alternate day oral steroids for Crohn's disease was measured by knemometry. Growth occurred on days free of treatment. This may represent a direct observation of the growth sparing effect of alternate day steroid medication.

The knemometer is designed to measure changes in tibial length with great accuracy.[1] The technique has recently been rigorously assessed and its power in detecting changes in growth over short (less than eight weeks) periods confirmed.[2] The definition of measurement is 0·1 mm and the coefficient of variation of six readings by one observer is 0·09% giving a precision (coefficient of variation × mean value of tibial length) of 0·2 mm. Intradaily variation in tibial length has been described in normal children,[3] and day to day fluctuations in growth shown in children receiving growth hormone using the same technique.[4]

The recent suggestion that this technique may be used as a sensitive marker of growth supression prompted us to measure the daily lower leg length of a child receiving alternate day oral steroids for the treatment of Crohn's disease.[5]

Case report

An 11·6 year old boy who had suffered from Crohn's disease for five years was an inpatient for establishment of an enteral feeding regime and exclusion diet He was otherwise in good symptomatic health with no clinical signs of relapse. He had received prednisolone intermittently since the onset of his illness and his height was on the third centile for chronological age, with a 2·5 year delay of skeletal maturation. His height velocity in the year before admission was 5·2 cm/year. After a three week period during which his dietary intake was stabilised his weight (on an Avery Beam Balance) and lower leg length were recorded daily one hour after waking and similar physical activity on the ward. Four measurements of lower leg length were taken at each attendance as previously described with no reference to the previous days readings.[2] The mean of the four determinations was used for comparison. Standing height was measured weekly using a Harpenden stadiometer For the final nine measurement days the soft tissue thickness of the heel pad and superior aspect of knee were measured to the nearest 0·1 mm using a linear ultrasound beam (Dermal Depth Detector, Cutech Ltd) to attempt to discriminate between true bone length change and soft tissue compression or expansion.

Throughout the measurement period the patient received 1g of sulphasalazine two times a day and 7·5 mg of soluble prednisolone on alternate days, after the measurement session. For the last week of study the steroid dosage was put 'out of phase' by one day to determine if any alteration in the pattern of growth could be observed.

Results

The changes in mean lower leg length, standing height, weight, and soft tissue thickness are shown in fig 1. It can be seen that there was consistent growth on days free of steroid, followed by a smaller shortening on treatment days. This pattern was maintained on and after the days when steroids were administered consecutively in the final week. This pattern can be quantified by comparing the changes in length observed from 'no treatment to treatment' days with 'treatment to no treatment' days and is significant (t=3·62; 13 df; p<0·005) (fig 2). The changes in weight tended to parallel the changes in lower leg length (on 11 out of 15 occasions) but the association was not significant (t=1·53; 13 df; p<0·2). Although the total soft tissue thickness varied from day to day, the changes were not significant and tended to oppose the length changes, supporting the observation that true lengthening of the lower leg occurred on steroid free days.

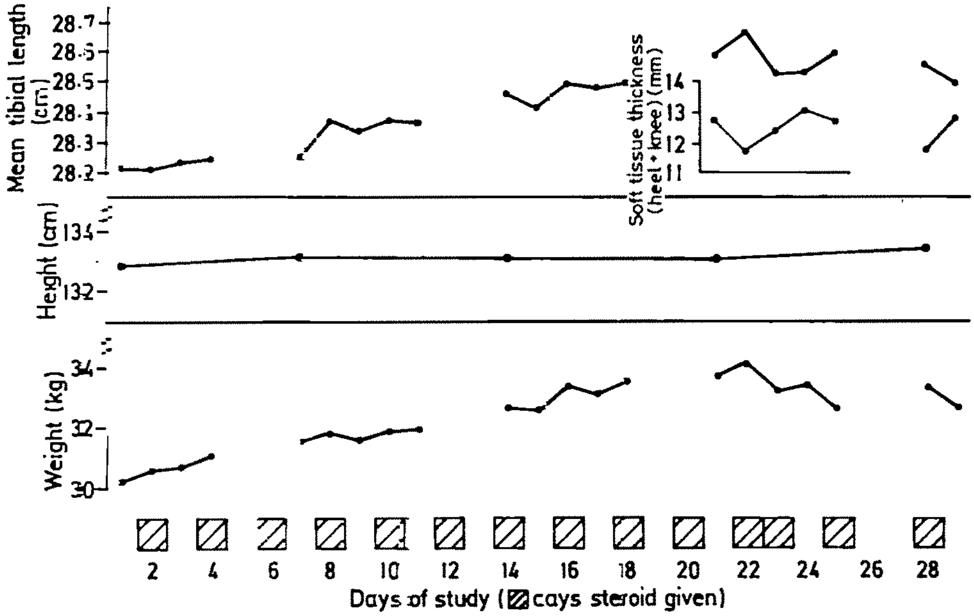

Fig 1 *Changes in mean tibial length, standing height, weight, and soft tissue thickness*

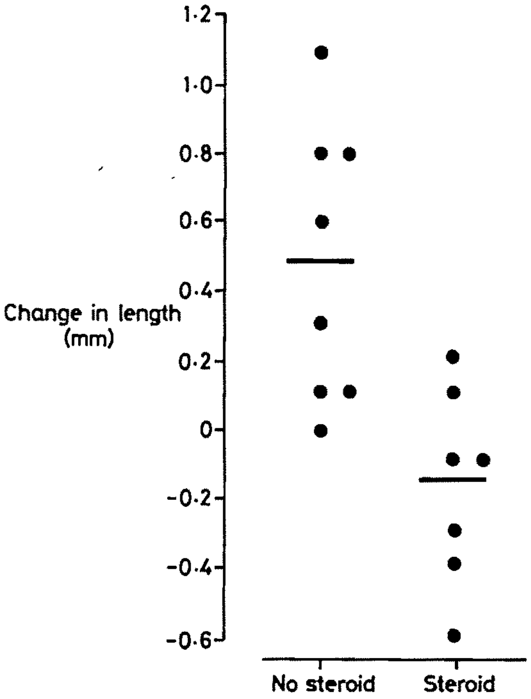

Fig 2 *Variation in lower leg growth with alternate day steroid treatment.*

Discussion

The knemometer provides a valuable means of observing biological phenomena related to short term, and ultra short term growth changes of the lower leg. The magnitude of the observed fluctuations in lower leg length in this case are well within the observed capabilities of the apparatus.[2] The mechanism of the growth inhibition due to steroid administration is uncertain but is probably secondary to a peripheral blocking of the action of growth hormone.[6] We postulate that the observed loss of length on days when steroids were administered is due to postural compression of non-growing cartilage and bone and is similar to the loss of length seen during illness or catabolic stress that we have previously described.[2] The observed differences in lower leg length probably do represent true changes in bone length rather than a soft tissue effect and could represent the first direct observation of the growth sparing effect of alternate day steroid regimes.

We thank Mrs M Pickering for performing the auxological observations.

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Rubella immunisation for girls over 14 years

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SUMMARY Rubella vaccination was offered to a cohort of schoolgirls 14 years and over whose immune state was unknown. This increased the percentage vaccinated or known to be immune from 86% to 90%. It is recommended that rubella vaccination should be offered to girls until they leave school at 16 years of age.

The uptake of rubella vaccine by schoolgirls has increased since 1976 but in most areas is still below 90%.[1] In inner city areas absenteeism, failure to return consent forms, intercurrent illness, parental refusal, and desire to attend their own general practitioner, have a negative influence on vaccine uptake.[2] High mobility of the population and administrative difficulties within schools are additional factors.

The schoolgirl rubella vaccination programme is offered to all girls between 11 and 13 years. It is then discontinued as girls aged 14 years and over must have preliminary screening for rubella antibody because of the risk of pregnancy.[3] The school health service has contact with girls until the age of 16, leaving two further years during which vaccination could be offered. This study describes a programme for schoolgirls, 14 years and over, to determine their immune state and subsequent acceptance of vaccination.

Subjects and methods

The subjects were girls in their third year at secondary school, 14 years old and over, who had not been vaccinated by June 1985, and who were attending the five local authority girls secondary schools in the Inner London Borough of Islington. Permission was obtained from each head teacher.

Details of rubella vaccination are normally entered in the school medical records (form 10 M) and school nurses keep a list of girls who do not attend. Using this information, the nurses identified the girls with unknown immune state and told them about the scheme. Parents gave written consent for serotesting and vaccination. An explanatory letter urging them to accept the programme was enclosed.

The school nurse arranged the session with clerical help and one clinical medical officer who took all the blood samples. Sessions or individual appointments were arranged depending on the number of girls. A thumb prick was made with an autolet and 0·5 ml of blood was collected into a plastic container. A venepuncture was offered but rarely chosen. The specimens were tested for rubella antibody by radial haemolysis at the local district general hospital and those with zone diameters corresponding to more than 15 IU/ml were considered immune.

Each girl was given a card with her rubella status and the parents were informed by letter. The school nurse arranged a time for the clinical medical officer to vaccinate those who were non-immune.

Results

In June 1985, 503 of 586 third year girls (86%) had a clear record of having been vaccinated between 11 and 13 years of age, the uptake varying from 72–100% between the five schools (table). Of the 83 girls who were still in school and whose immune state was unknown, 56 (67%) were offered the programme. Out of these 56 girls, 25 (45%) accepted. All but four were seropositive and these four girls were vaccinated. Thus by the end of the programme 528 (90%) of third year girls had either been vaccinated or were known to be seropositive.

Discussion

It is a matter of urgency to increase rubella vaccination uptake in schoolgirls. Introduction of the triple measles, mumps, and rubella vaccine will still require further selective vaccination unless childhood uptake levels are raised rapidly.[4]

The different uptakes between the schools largely reflect the enthusiasm of the individual school nurses as the school populations are similar. School 5 had already achieved 100% uptake in those under 14 years of age because of the nurse's persistent efforts.

The 'sweeping-up' programme was offered to all the 19 eligible girls in school 2, while in schools 1, 3, and 4 it was offered to 24 (59%), six (55%), and seven (58%) of those eligible, respectively. The nurse needs to be highly motivated to keep her own records up to date, to search through the school medical records, and look for missing records when the mobility of the population is estimated at 20%. Girls often playing truant makes contact very difficult.

The nurse in school 2 was particularly successful and enthusiastic because of the poor uptake between 11 and 13 years (72%). In her school a higher proportion of eligible girls participated in this programme than in schools 1, 3, and 4. Non-participants included truanters, refusers, and failures

Table *Outcome of rubella vaccination programme in girls, 14 years and over, attending the five schools studied*

	Schools					
	1	*2*	*3*	*4*	*5*	*Total*
Total No of girls on roll	253	69	88	93	83	586
No who were vaccinated at 11–13 years (%)	212 (84)	50 (72)	77 (88)	81 (87)	83 (100)	503 (86)
No with unknown immune status	41	19	11	12	0	83
No who were offered programme	24	19	6	7	0	56
No who participated	10	10	3	2	0	25
Total vaccinated or known immune after programme (%)	222 (88)	60 (87)	80 (91)	83 (89)	83 (100)	528 (90)

to return consent forms. Consent was asked for both serotesting and vaccination, although some parents may have preferred to decide about vaccination once the immune state was known. Starting this programme earlier in the term may have given more time for follow up, including personal contact by phone or home visits.

All those who wanted to participate were able to as the clinical medical officer went to the school on an individual basis, rather than for an immunisation session. For example, two girls were vaccinated after they signed the morning register and before they played truant that day. In agreement with others,[5] the finger prick was found to be acceptable to most schoolgirls and allows easy collection of blood for serotesting.

In girls 14 years and over serological testing is currently recommended because of the risk of unnecessarily vaccinating a pregnant woman. Recent studies have not been able to show an association between congenital rubella syndrome and vaccination during pregnancy or before conception.[6] Schoolgirls who play truant are likely to miss vaccination and may be at risk from an unplanned teenage pregnancy.

Although only four non-immune girls were identified, all were subsequently vaccinated, and the percentage of those known to have been vaccinated or immune increased from 86% to 90%. It is better to vaccinate late in secondary school than to rely on girls attending their general practitioner or antenatal clinic. As schoolchildren are accessible by the school health service until they are 16 years old, it must be the responsibility of each community paediatrician to continue the rubella vaccination programme beyond 13 years of age, even though it involves serological testing to fall within the Joint Committee on Vaccination and Immunisation guidelines.

I thank the school nurses, Dr MC Kelsey, microbiology department, Whittington Hospital, London for help and Dr CL Miller and Dr ON Gill, Public Health Laboratory Service Communicable Disease Surveillance Centre, London for their advice

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British Paediatric Association

Annual meetings

At York University:
1989 April 11–14

At University of Warwick:
1990 April 3–6
1991 April 16–19
1992 April 7–10
1993 April 20–23 (provisional)
1994 April 12–15 (provisional)

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Controversy

Ribavirin in respiratory syncytial virus infection

A double blind placebo controlled trial is needed

At a recent workshop on infection the indications for ribavirin were discussed. Ribavirin has recently been licensed for hospital use in the United Kingdom having previously been available only on a named patient basis. Nebulised ribavirin is being vigorously promoted by the United Kingdom marketing company, Britannia Pharmaceuticals, for selected use in respiratory syncytial virus infections largely based on the 1985 guidelines of the American Academy of Pediatrics (AAP).[1] The AAP suggest that nebulised ribavirin should be considered for the following patients with proved infection by respiratory syncytial virus.

(1) Patients at high risk: infants with congenital heart disease, bronchopulmonary dysplasia and other chronic lung conditions, certain premature infants, children with immune deficiency (especially severe combined immune deficiency), recent transplant recipients, and those on chemotherapy for malignancy;

(2) Severely ill infants: those with PaO_2 concentrations of <8·66 kPa or rising $PaCO_2$ concentrations;

(3) Infants with mild disease which may progress: infants under 6 weeks of age and those with an underlying condition such as multiple congenital anomalies, neurological or metabolic diseases.

Although one of us has previously reached similar conclusions to the AAP[2] we are concerned that the climate of opinion, certainly in the United States, is tending to imply that the case for ribavirin is proved and clinical trials are no longer ethical.

There is evidence that infants with congenital heart disease[3] and children with compromised immunity[4] have an increased mortality from respiratory syncytial virus infection. The severity of the infection in preterm infants and the degree to which the lower respiratory tract is affected seems to increase with postnatal age.[5–7] In one study four of 25 neonates who contracted respiratory syncytial virus died, two of them suddenly and unexpectedly, although the role of the virus was unclear.[6]

The mortality of full term infants without underlying disease who are hospitalised with respiratory syncytial virus infection is less than 1%.[6] Controlled trials of the use of ribavirin in such infants show modest improvement in clinical parameters and oxygenation,[8–11] which although statistically significant is of doubtful clinical significance. Nasal shedding of respiratory syncytial virus was reduced in only one of the four studies and may anyway not reflect bronchiolar titres of the virus.[8] The total number of treated infants in the four controlled trials is 62. No children in treatment or control groups died and there was no reduction in hospital stay in the only study which recorded this.[11]

MacDonald *et al* reported a mortality of 37% in infants with congenital heart disease and infection with respiratory syncytial virus,[3] but Hall *et al,* in a prospective trial, reported that none of seven infants with congenital heart disease or bronchopulmonary dysplasia, or both, who received placebo and none of six who received ribavirin died.[12] It is possible that earlier recognition and improved conventional, supportive treatment of respiratory syncytial virus infection in infants with cardiopulmonary disease may be more important than any antiviral treatment.

There are anecdotal reports of nebulised ribavirin clearing persistent respiratory syncytial virus and parainfluenza virus infections in immune deficient children who could subsequently receive bone marrow transplants.[13 14] Such children are few in number and a controlled trial would be impractical. Most would agree that infection by respiratory syncytial virus in a child with severe immune deficiency is an indication for ribavirin treatment, but there is no evidence that children on chemotherapy for malignancy are helped by ribavirin.

To our knowledge there is no firm evidence that ribavirin reduces mortality, even in 'high-risk' groups, nor that it obviates the need for artificial ventilation or reduces duration of hospital stay.

Ribavirin may prevent long term morbidity, but the results of trials are awaited. There is insufficient experience on which to base assertions of its safety, particularly with regard to long term toxicity. The cost in the United Kingdom is just over £500 for the recommended three-day course.

In our opinion the only way to resolve our doubts is a multicentre, double blind, placebo controlled trial of nebulised ribavirin for infants with pre-existing cardiopulmonary disease and babies under 6 weeks old who develop proved respiratory syncytial virus infection. The main hypotheses to be tested are that nebulised ribavirin reduces the need for artificial ventilation, shortens hospital stay, and reduces mortality in one or both of these two groups. Pending the results of such a trial we would respectfully urge paediatricians to be circumspect in the use of an expensive drug that we do not feel has been proved to be of undoubted benefit. Our efforts in the interim would be better directed towards prevention of nosocomial respiratory syncytial virus infection, particularly of high risk patients, by improved handwashing and other infection control measures, and towards early identification and supportive treatment.

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Reply from Dr Snell:

I am grateful for the opportunity to respond to the thoughtful article from Dr Isaacs and his coauthors regarding the use of nebulised ribavirin in respiratory syncytial virus infection In essence, they express doubts regarding the value of ribavirin and feel that a further large scale clinical trial should be carried out, in infants with pre-existing cardiopulmonary disease and neonates ('high risk infants'), in order to convince them of the efficacy of ribavirin in this situation.

The authors review only four published studies, including 62 treated infants, implying that no other data are available. This is not the case, as published data are available which document at least 175 infants treated with ribavirin, 128 in double blind, controlled clinical trials, and all these papers were made available to Dr Isaacs. In addition, further studies have been carried out which are not yet published.

The United States and the United Kingdom licensing authorities, who had access to all the existing data, published and unpublished, have granted product licenses for nebulised ribavirin in the treatment of infants and children with severe infection by respiratory syncytial virus. In so doing they have accepted the efficacy of the drug (in comparison with placebo) and its safety (as judged on a risk/benefit basis). The trials completed to date have shown statistically significant improvements in comparison with controls, in severity of illness,[1–4] signs and symptoms,[1 3 5–7] resolution rate,[3 7] oxygen saturation,[1–3] need for supplemental oxygen,[8] days requiring assisted ventilation,[8] need for therapeutic interventions,[7] duration of viral shedding,[1 2 9] and IgE response to infection [10] No serious toxicity was ascribed to ribavirin in any of the published reports, controlled[1–10] or open,[11–14] and none has been reported to the United States Food and Drug Administration, although some 30 000 infants have now received nebulised ribavirin treatment.

To clarify one specific point that has been raised;

in the study of Hall *et al* of 'high-risk' infants,[2] those infants considered to be at highest risk were *not* entered into the placebo controlled study (this was not considered acceptable), but treated openly with ribavirin. Thus the study population was not analogous to the group in which a 37% mortality had previously been shown. It may be noteworthy, however, that all these infants most at risk, who all received ribavirin, survived, in contrast with previous experience.

Dr Isaacs and his coauthors consider that a further placebo controlled study should be carried out in 'high-risk' infants to assess effects on need for assisted ventilation, duration of hospital stay, and mortality Beneficial effects on the first two of these parameters have already been shown (unpublished data)[8] and are being addressed again in a large scale study which is planned to take place in the United Kingdom (*not* in high risk infants) in the next winter season. This study includes a one year follow up to assess both long term benefit and any long term adverse effects; again, Dr Isaacs was made aware of this planned study before finalising the article for the *Archives*.

Beneficial effects on mortality can only be shown, by definition, if a number of infants in the placebo group die. For this reason, I cannot accept that it is ethical to carry out a placebo controlled study in high risk infants, where half the patients would be denied a treatment whose beneficial effects have already been shown (and accepted by several very critical licensing authorities) in the expectation that some would die. I very much doubt that such a study design would be acceptable to any local ethical committee, nor can I believe that any parent could give a truly informed consent for their sick child to participate in such a study under these circumstances. The feeling that further placebo controlled trials would not be ethical has been expressed by other experienced researchers in this field,[7] and recent informed opinion appears to support the view that the efficacy of ribavirin in infants with cardiopulmonary disease is proved and that all such infants hospitalised because of respiratory syncytial virus infection should receive ribavirin treatment.[15]

I see no ethical dilemma, however, in carrying out randomised, placebo controlled studies in subjects who are not severely ill and do not fall into one of the 'high risk' categories, in whom morbidity will be low and mortality should be zero, provided these are designed to address sufficiently important questions relevant to the mode of action of the drug, its safety and efficacy.

Future research approaches could usefully include studies of modified dosage regimens: animal data suggest that increasing the dose of ribavirin in the aerosol and shortening the duration of administration may produce equivalent therapeutic benefit to the currently recommended schedule.[16]

No one could argue with the author's final statement that efforts should be directed towards prevention of nosocomial infection by respiratory syncytial virus, but the real question is whether effective treatment should be withheld from those infants who, despite all control measures, contract severe disease. Here, I would fully agree with the opinion recently expressed by Dr Isaacs himself: '. . . In infants with cardiopulmonary disease and respiratory syncytial virus infection, there is clear evidence of clinical benefit and minimal toxicity . . . I believe nebulised ribavirin is indicated in such children'.[17]

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Randomised trials and ribavirin

'Uncertainty' about whether to use a treatment is the basis of all randomised controlled trials. Indeed, it can be argued that it is unethical *not* to randomise when there is uncertainty because this ensures that only 50% of current patients will receive whichever turns out to be the worse management, quite apart from the benefits which accrue to those who have the illness in the future.

Should paediatricians be uncertain whether or not to use ribavirin? The articles on the previous pages certainly suggest that there are widely varying beliefs about the place of this new drug in everyday practice, and variations in practice are a measure of 'collective' uncertainty. Individually, paediatricians should decide by critically appraising the evidence which is 'in the public domain' for themselves. (There are understandable commercial and other reasons why a company may choose not to publish data about a new product, but Dr Snell must recognise that these data cannot then be used as 'public' support for the product). Most weight should be given to the *randomised* controlled trials. The weakness of using historical controls is illustrated by the apparent change over time in the risk of death due to respiratory syncytial virus in infants with congenital heart disease treated conservatively. Comparisons using concurrent but non-randomised controls are also highly prone to bias. The five properly reported randomised controlled trials included only 76 children treated with ribavirin. They are 'efficacy' or 'explanatory' (*can* it work?) trials. That is to say, small numbers of patients were investigated in a tightly controlled environment and outcome was assessed by short term surrogate measures such as illness severity scores and arterial oxygen concentrations These trials do suggest a benefit in these respects, but the clinical significance of this is unclear, particularly in the longer term. Dr Isaacs and his colleagues (p 986) call for a much larger 'effectiveness' or 'pragmatic' (*does* it work?) trial to assess ribavirin in everyday practice in terms of clinically more meaningful outcomes such as length of time on a ventilator and length of stay in hospital Improvement in these terms could offset the high financial cost of treatment.

The possibility of unanticipated adverse effects of ribavirin must also be included in the appraisal. It is reassuring that licensing authorities in the United Kingdom and the United States have given ribavirin a (limited) licence, because these authorities are primarily concerned with drug safety Nevertheless, the Committee on Safety of Medicines has made special reporting a requirement for ribavirin and the marketing data sheet does mention the possibility of serious side effects in the short term. Furthermore, larger numbers of children must be followed up for much longer before rare, but serious, long term adverse effects can be ruled out with any confidence.

On the basis of the limited evidence currently available paediatricians are likely to come to differing conclusions about the effectiveness and safety of ribavirin. Some may feel that ribavirin must be used in some clinical situations, others may conclude that on present evidence, it has no place in everyday practice. But I suspect that many will be uncertain whether they should use ribavirin for respiratory syncytial virus infection, even for children who are most severely affected or most at risk. If so, this uncertainty can only be resolved by large 'pragmatic' randomised controlled trials as called for by Dr Isaacs and his colleagues.

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Response

Dr Snell reaches different figures from us on the number of children who have received ribavirin in controlled trials because of our different interpretation of what constitutes a quotable controlled trial. But this is quibbling: our point was that thousands have been treated on the basis of relatively little controlled data. To use the granting of a product licence by licensing authorities as evidence of efficacy is novel but scientifically unacceptable.

We do not believe that Dr Snell has refuted our three main points, namely that there is no evidence for ribavirin decreasing the need for artificial ventilation, reducing hospital stay, or reducing mortality. In attempting to refute the first two points, he quotes a 1985 meeting abstract never published as a paper and 'unpublished data'.

Dr Snell's argument that it would be unethical to test the hypothesis that ribavirin saves lives because babies would die in the trial is an old one and has been used in the United States.[1] It presupposes that ribavirin *does* save lives. If this is the case, then a trial will prove to all doubting paediatricians, including the authors of this letter, that the drug should be used for 'at risk' patients. But ribavirin may conceivably increase mortality by aggravating bronchoconstriction or by precipitating in ventilator tubing. A significant reduction in the need for artificial ventilation in 'at risk' infants would, however, be an important finding which might justify early use of ribavirin in such infants. Until this evidence is available, however, we do not consider the routine use of ribavirin in 'at risk' infants to be justified just because ribavirin *may* be useful. Dr Snell's proposed large scale study on low risk infants does not address these points.

Although one of us previously suggested that ribavirin was indicated in some 'at risk' infants, he also suggested that further controlled trials are needed.[2] Ribavirin has not been used in Oxford and there have been no deaths from respiratory syncytial virus infection in the last three years although 16 babies have required artificial ventilation. We are alarmed that in the United States ribavirin is widely used even for low risk infants, but would note that Ellen Wald and colleagues at Pittsburgh have recently come to very similar conclusions to us regarding the inappropriateness of treating low risk infants with ribavirin, the paucity of controlled data on high risk infants, and the need for large, controlled clinical trials.[3]

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Personal practice

Renal failure in the newly born

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When urine output is absent or reduced and azotaemia develops renal failure is said to have occurred. It is acute if it happens over a period of days or weeks and chronic, often irreversible, when it takes months or years. Renal failure in the newly born infant is unique as it occurs after a period of intrauterine life and in a setting of immature renal function so that renal failure due to major anatomical abnormalities such as renal agenesis can present in the newborn as an acute problem

During intrauterine life the placenta performs all the excretory functions necessary to maintain normal fetal homoeostasis. The primary function of the kidney is the maintenance of normal amniotic fluid volume and the overall renal function of the fetus is low. Even when there is bilateral renal agenesis, azotaemia does not become evident until sometime after birth. At birth glomerular filtration rate averages 0·84 ml/minute/kg. It increases rapidly and doubles by the third week of life as the perfusion and function of the superficial cortical nephrons increases with greater renal plasma flow.[1 2]

All functions of the kidneys of normal newborn infants operate very close to their maximum capacity. Under normal circumstances in a healthy infant this is not clinically important but there is a limited ability to vary renal function in response to stress.

It has been recognised for many years that a newborn has a limited ability to excrete a sodium load.[3] This is probably due to enhanced distal tubular sodium reabsorption and high plasma aldosterone concentrations.[4] In contrast the immature kidney loses salt and premature infants often become hyponatraemic due at least in part to immaturity of the tubular glomerular feedback mechanism.[5]

In response to severe dehydration the newborn kidney is unable to increase urine osmolality above 700 mmol/kg. This is largely due to the concentration of urea in the renal medulla.[6] The ability to concentrate the urine increases with dietary protein intake. Conversely the newborn has an impaired ability to excrete large amounts of free water particularly during respiratory distress syndrome.[7]

It is also well known that the newborn easily becomes acidotic in stressful situations This is mainly due to immaturity of net acid secretion.[8] Consequently these infants are more susceptible to the metabolic insults associated with increased acid load and are unable to maintain normal homoeostasis under stress.

Diagnosis

The cardinal feature of acute renal failure is azotaemia with or without oliguria.

Blood urea concentration is influenced by many extrarenal factors including dehydration and protein catabolism, and the plasma creatinine concentration is a more reliable index of glomerular function. At birth the plasma creatinine concentration (measured by the kinetic Jaffe reaction) approximates to that of the mother and ranges from 17 to 188 μmol/l. The concentrations fall rapidly and by the second week average 35 μmol/l.[9] Interpretation of a single plasma creatinine concentration during this time is further complicated by analytical interferences caused by unconjugated bilirubin (causing falsely low concentrations), ketones, and many drugs—for example, cephalosporin (which causes falsely high concentrations). For these reasons plasma creatinine rising consistently by more than 20 μmol/l/24 hours is more important than a single high concentration.

The onset of urine flow in term babies is variable but is normally within the first 48 hours. Undetected spontaneous voiding during delivery may explain apparent anuria. Oliguria in the neonate is generally defined as a urine flow less than 0·5 ml/kg/hour. It is important to recognise, however, that renal failure can occur with normal urine flow rates of between 1–3 ml/kg/hour. The table shows a checklist of information that is needed in evaluating oliguria.

Haematuria is an unusual finding in the normal newborn, although about 10% will have a result of up to 1+ on dipstick testing (equivalent to 10 red blood cells/μl). Proteinuria is rare but when it is present it is abnormal if the result on dipstick

Table *Information required when evaluating oliguria in neonates*

Clinical:	Daily fasting weight Blood pressure Evidence of infection Drugs (a) nephrotoxic—treatment stopped (b) excreted by the kidney—dose adjusted
Urine:	Flow rate (ml/kg/hour) Routine urinalysis—blood, protein, microscopy Sodium, creatinine, and urea concentrations, osmolality Culture
Blood:	Urea, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, and glucose concentrations, osmolality Culture Arterial pH
Others:	Chest x ray Renal ultrasound

testing is greater than 2+.[10 11] False positives for protein may occur when specimens are collected in vessels containing residual disinfectants based on quarternary ammonium compounds or chlorhexidine. Urine microscopy is important to identify red cells and casts. Red cell and granular casts may be seen in normal urine but more than one per high power field is abnormal.[10] Careful microscopic examination of the urine particularly for frequent broad cast, red cells, and significant proteinuria are important features of parenchymatous renal disease.[12]

Chemical analysis of the urine has also been suggested to help distinguish between parenchymatous renal failure and decreased renal perfusion. The most generally used indices are the fractional excretion of sodium (FE_{Na}):

$$FE_{Na}=\frac{\text{Urine sodium}\times\text{plasma creatinine}}{\text{Plasma sodium}\times\text{urine creatinine}}$$

and the renal failure index (RFI)

$$RFI=\frac{\text{Urine sodium concentration}\times\text{plasma creatinine}}{\text{Urine creatinine}}$$

Normal values for both are the same and a renal failure index or fractional excretion of sodium greater than 3 is said to suggest parenchymatous renal failure. A urine to plasma osmolality ratio of less than one has been found in newborns with renal failure and may be helpful in distinguishing acute renal failure from the syndrome of inappropriate antidiuretic hormone.[3] The results of these indices are usually difficult to interpret, however, due to the effects of the immaturity of the urinary concentrating mechanism, the effects of low protein diet on urine osmolality, and the high urinary sodium excretion in premature babies.[5] More often than not the diagnosis of parenchymatous renal failure or hypovolaemia is made on the basis of sound clinical judgment supported by simple urine analysis and microscopy. The diagnosis of hypovolaemia may be suggested when the blood urea is raised out of proportion to the plasma creatinine concentration. The urine indices are often unhelpful. The diagnosis may be further complicated by the knowledge that hypovolaemic renal failure may progress to renal parenchymal failure.

Incidence

It is difficult to estimate the true incidence of acute renal failure in the neonate. It has been calculated that 6% of babies admitted to one neonatal intensive care unit had renal failure.[14] In the Yorkshire region an average of seven newborn babies are dialysed each year because of acute renal failure (0·2 per 1000 live births) but many more are managed conservatively and not referred for dialysis treatment. This comprises 25% of all children dialysed in the Yorkshire region for acute renal failure each year.

Aetiology

Because of the unique circumstances of the newborn, major anatomical abnormalities of the kidneys and urinary tract may present as acute renal failure.

Bilateral hydronephrosis due to urethral valves can now be detected by skilful antenatal ultrasound examination of the fetus and as a result it is no longer the acute medical problem it was. Bilateral renal hypoplasia or dysplasia may not progress to renal insufficiency until several weeks after birth, although in severe cases the features of Potter's syndrome or pulmonary dysplasia will be immediately apparent.

Aggressive modern intensive care has resulted in the resuscitation of many ill newly born term and extremely premature infants. In these children the aetiology of acute renal failure is often complex. Respiratory distress syndrome appreciably depresses glomerular filtration rates,[7] and renal failure develops after severe asphyxia.[12] Renal venous thrombosis may complicate any severe illness in the newborn particularly if there is a history of sepsis, maternal diabetes, or prediabetes. Undetected hypotension in the baby after antepartum haemorrhage and septicaemia, particularly if treated injudiciously with nephrotoxic antibiotics, are also important causes. Congenital heart disease is the single commonest abnormality associated with acute renal failure. In the Yorkshire region it accounts for 25% of the babies with renal failure in the first month of life. Anomalies with left ventricular outflow tract obstruction or a prolonged period of cardiopulmonary bypass are associated with increased risk.[15]

Management

A successful conclusion to the management of renal failure in the neonate requires ready access to the expertise of a neonatal intensive care unit and the combined skills of a neonatologist, paediatric nephrologist, surgeon, radiologist, and biochemist. It is unwise to attempt treatment without this team.

Obstructive uropathy and other anatomical anomalies of the urinary tract must be excluded by an abdominal ultrasound examination and the bladder catheterised with a fine feeding tube. This also allows the accurate measurement of the urine flow rate facilitating fluid balance management. If there is doubt about the extent of a prerenal component then there are those who suggest a fluid challenge of 10 ml/kg of isotonic sodium chloride solution over an hour[16] or a mannitol infusion.[7] Both are potentially dangerous and should only be done when there is ready access to dialysis. The use of frusemide 1 mg/kg body weight has been well established in the treatment of acute renal failure in adult patients but there is no evidence of its value in the newborn.[17] It does have the virtue, however, of being relatively safe. If in doubt it is much wiser to restrict fluids from the baby for 24 hours by which time the diagnosis is usually more clear.

Meticulous attention to the details of fluid and electrolyte balance are fundamental. Water losses from urine, gastrointestinal loss, and urine output should be calculated and replaced. The insensible water loss of a normal newborn is estimated to be 50 ml/kg/day.[18] One third of this is respiratory loss, which is negligible during artificial ventilation. Insensible fluid loss is 30% greater under radiant heat incubators than in conventional incubators.[19] Sodium or potassium replacement are usually unnecessary in oliguric renal failure unless there are appreciable gastrointestinal losses, but correction of the acidosis is important. This requires a combination of skilful ventilation and sodium bicarbonate supplementation to keep the blood arterial pH as near normal as possible. The amount of bicarbonate required varies depending upon the severity of the acidosis but it should be remembered that one mmol of sodium is given with every mmol of bicarbonate, and the infusion of bicarbonate carries several risks including cerebral haemorrhage. Severe acidosis in renal failure is often best treated by early dialysis.

The strict fluid restrictions seriously limit a baby's nutrition, and hypoglycaemia is a common complication. A vigorous attempt to maintain a caloric intake of at least 0·21 MJ/kg/day should be made if necessary by parenteral nutrition. This may be difficult within the restrictions imposed by the fluid allowance and early dialysis treatment is often necessary so that adequate nutrition can be maintained.

Poor nutrition leads to catabolism, which aggravates the acidosis and hyperkalaemia Conservative measures to lower plasma potassium concentrations with glucose infusion (insulin often induces severe hypoglycaemia and is not recommended) or ion exchange resins (1 g/kg body weight in a 10% mannitol solution) are effective for only a few hours and are at best temporary measures while preparation is made for dialysis. Hypocalcaemia and hypomagnesaemia are frequent findings in acute renal failure,[20] and potentiate the toxic effects of hyperkalaemia on the heart. It is important to maintain plasma concentrations of calcium and magnesium within the normal ranges with 10% calcium gluconate (0·5–1 ml/kg over two minutes)

The drug chart should be examined, nephrotoxic drugs stopped and those known to be excreted by the kidney carefully controlled by frequent measurements of blood concentrations whenever possible

Infection is often associated with acute renal failure either as a cause or a complication and should be excluded by urine and blood culture.

Dialysis treatment is indicated when there is fluid overload, severe acidosis (pH less than 7·2), hyperkalaemia, and progressive uraemia. Fluid overload when associated with gross peripheral oedema, hypertension, or pulmonary oedema requires treatment by early dialysis. It is often necessary to remove fluid to 'make room' for infusions of ionotropic drugs, blood, nutrition, or other essential supportive drugs. Severely ill oliguric newborn infants readily become acidotic. Sodium bicarbonate infusion can be hazardous in these circumstances and it is wiser to initiate dialysis treatment early rather than infuse bicarbonate, which will result in further fluid overload

A plasma potassium concentration of 6·0 mmol/l or more and a blood urea of greater than 10 mmol/l that is rising by more than 6 mmol/l a day indicates catabolism and rapidly progressing uraemia, and it should prompt referral for dialysis treatment.

Peritoneal dialysis is the method of choice in the neonate It is a simple technique but not without difficulties even in the most skilled and experienced hands. The most often encountered complications are failure to achieve satisfactory drainage of dialysate and peritonitis. There is a risk of perforating a major vessel in a paralysed baby on a ventilator. Water and urea are removed efficiently and in most cases the acidosis improves rapidly, but occasionally it does not. This is probably because standard peritoneal dialysis solutions have lactate as the source of bicarbonate. Some infants, especially those with a severe lactic acidosis, are unable to metabolise it and remain acidotic despite dialysis A bicarbonate dialysis solution would be preferred, but is not manufactured, and an acetate solution, which has some theoretical advantages, is no longer manufactured.

Haemodialysis is difficult in the newborn but may be necessary if peritoneal dialysis is not possible because of abdominal surgery or other technical difficulties. Vascular access is usually achieved by a Hickman line inserted in the external jugular vein. Treatment is usually for two to three hours at a time.

Continuous arteriovenous haemofiltration is being used increasingly in the newborn.[21] This method requires the catheterisation of an artery (usually the femoral or umbilical arteries). The blood passes continuously, often for 24 hours or more, across a small haemofilter comprising a number of hollow fibres, and is then returned to the baby's veins. The filtrate that is produced is measured, discarded, and simultaneously replaced by an appropriate volume of electrolyte solution. It is a gentler procedure than haemodialysis and we have found it to be a simple and effective alternative to peritoneal dialysis, particularly in babies with renal failure after cardiac surgery.

Prognosis

The prognosis reflects the nature of the underlying cause of acute renal failure. Three quarters of those who develop renal failure after perinatal anoxia survive but 40% of the survivors had either cerebral or renal damage.[12] In contrast 75% of newborns who had renal failure after cardiopulmonary bypass surgery died and 50% of the survivors had neurological damage.[15]

During the last two years we have dialysed 14 neonates. Eight had medical causes of renal failure: four after sepsis, two after hypovalaemic shock from antepartum haemorrhage, and two because of prematurity and asphyxia; of these two died. In contrast six neonates were dialysed after surgical procedures for congenital anomalies: three after cardiopulmonary bypass surgery, two with diaphragmatic herniae, and one with prune belly syndrome with renal dysplasia; of these three died.

Up to 40% of the survivors may have decreased creatinine clearances and a smaller proportion will have a renal tubular acidosis or a concentrating defect indicating residual renal tubular dysfunction.[12]

The increasing vigour with which neonatal intensive care is being applied has resulted in an increase in acute renal failure. Treatment is a challenge and can be rewarding as the results and techniques improve. One must be constantly mindful, however, of the painful consequences of the long term neurological and renal complications before embarking upon a course of treatment that can be difficult to stop.

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Archives of Disease in Childhood, 1988, **63,** 995–1000

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Tuberculosis in children

Sir,

We were interested to read the two articles recently published in *Archives* from the Medical Research Council Tuberculosis and Chest Disease Unit[1] and Packe and Innes [2] We were particularly interested in the comments on tuberculous meningitis in children.

We have recently reviewed the cases of tuberculous meningitis seen at the Royal Hospital for Sick Children, Glasgow.[3] Between 1968 and 1986, 15 children were seen because of this condition Fourteen were white and only one was Asian The mean age at presentation was 2 years (12 months to 12 years) and none had received BCG vaccination In 12 children close contact with other cases of tuberculosis was identified

It is clear that the practice of offering BCG vaccination to children at 13 years of age was too late to protect the children we studied from acquiring the infection Routine BCG vaccination of all neonates was stopped in Glasgow in 1974 and since then has been offered only to babies of Asian or Chinese origin. This may partly explain why most cases of tuberculous meningitis seen in our hospital occurred in white children

We agree with the recommendation of the World Health Organisation that the use of BCG vaccination should be as early in life as possible and stress that any abandonment of such policy must be accompanied by meticulous case reporting and contact tracing if more cases of this serious condition are to be avoided.

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Total parenteral nutrition and sepsis

Sir,

The paper by Dr Beganović and colleagues on total parenteral nutrition and sepsis contributes little to our understanding of either of these issues.[1] Sepsis was considered proved by positive bacteriology in 13% of infants receiving total parenteral nutrition and 6% of those who did not (the percentages given in the table have been miscalculated) Eighty per cent of blood cultures grew *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli* or group B streptococcus, important causes of serious infection in the newborn period, puzzlingly described by the authors as 'fairly benign'

We are not told the proportion of patients with a central venous catheter for total parenteral nutrition and those fed through a peripheral venous cannula The effect that this might have had on sepsis rates within the group receiving total parenteral nutrition is of considerable practical importance Patients receiving total parenteral nutrition were almost certainly more likely than enterally fed infants to have other sources of infection such as arterial catheters, endotracheal tubes, chest drains, etc. The lack of information relating to primary and secondary catheter sepsis makes it impossible to assess objectively the risk of infection related directly to administration of total parenteral nutrition.

The authors conclusion that 'the advantages of total parenteral nutrition outweigh the disadvantages of sepsis in this group of infants' is extraordinary as no details of the advantages derived from total parenteral nutrition or the morbidity and mortality associated with sepsis are given. The fact that 64% of the study population received total parenteral nutrition indicates an astonishingly high proportion of neonates in whom enteral nutrition was considered to be contraindicated.

We suggest that the frequent recourse to total parenteral nutrition as highlighted in this study does not reflect 'the fact that the commercially available solutions have been adapted from premature newborn infants' so much as an uncritical approach to the use of a valuable treatment, but one which despite the authors opinions has a more limited application than they imply

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Drs Verloove-Vanhorick and Beganović comment.

Dr Puntis misunderstood our paper on total parenteral nutrition Our aim was, foremost, to provide data on total parenteral nutrition and sepsis in a relatively huge cohort of *very* low birthweight or *very preterm* babies. Obviously, in such a nationwide, collaborative epidemiological study in a high risk population a single aspect of perinatal care cannot be recorded exhaustively. Dr Puntis' criticism on lack of certain data seems therefore unwarranted Some points, however, may easily be clarified.

'Clinical sepsis' was considered to be present if clinical and/or haematological signs were recorded. If, in addition to these, a positive blood culture was recorded, the sepsis was defined as 'bacteriologically confirmed'. Central catheters were used only sparingly in the Netherlands, and total parenteral nutrition was administered mostly by peripheral infusion. Blood cultures were seldom taken routinely, even in infants treated by total parenteral nutrition. Only clinical evidence of sepsis justifies such a procedure in these very small infants.

Dr Puntis misread the part about causative organisms. Far from considering these benign, we stated that in infants treated by total parenteral nutrition the causative organisms were 'fairly benign' namely, compared with infants not treated by total parenteral nutrition, this point is illustrated even better by our original unpublished table, categorising the causative organisms by duration of total parenteral nutrition (see table).

Table *Causative organisms of bacteriological sepsis by duration of total parenteral nutrition, as percentage of cases in each group*

Duration of total parenteral nutrition (days)	*S epidermidis*	*S aureus*	*E coli*	*Streptococcus group B*	*Other*
0	4	11	25	29	32
1–7	27	19	19	16	19
8–28	36	26	20	7	11
>28	67	17	—	—	16

Quite correctly, Dr Puntis points out that no conclusion can be drawn from our data as to the aetiology of sepsis related to total parenteral nutrition. As the administration of total parenteral nutrition, however, both by peripheral and by central systems, carries the risk of introducing micro-organisms by infected fluids[1] or systems,[2] a causal relation is plausible. In addition to the strong association between sepsis and total parenteral nutrition emerging from our multivariate statistical analysis this justifies our conclusion that total parenteral nutrition is an important risk factor for sepsis in such infants

We do not share Dr Puntis' view that total parenteral nutrition was overused. The study population contained, by definition, almost exclusively infants with immature digestive systems, which renders non-use of total parenteral nutrition the exception. Next to recent improvements in ventilatory support systems, total parenteral nutrition as the source of adequate nutrition is one of the most obvious factors contributing to the trebled rate of intact survival of such infants in the past 20 years [3]

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Plasma amino acids in preterm infants fed on human milk or formula

Sir,

We read with interest the paper by Ventura and Brooke and were surprised that they stated there were few data on amino acid concentrations in babies fed the new low birthweight formulas or on babies fed breast milk.[1] Two years ago we published amino acid profiles on 85 low birthweight infants as part of a randomised controlled trial comparing different low birthweight formulas and expressed breast milk [2] Like Ventura and Brooke we found higher total amino acids in low birthweight babies fed formulas compared with those fed breast milk, but we also showed different concentrations of three amino acids depending upon type of low birthweight formula (table).

Table *Comparison of selected amino acids in formula fed babies. Results are mean (SD)*

Amino acid (μmol/l)	*SMA LBW (n=25)*	*Prematalac (n=25)*	*Preaptamil (n=25)*
Phenylalanine	45 (9)	56 (15)	53 (22)
Cystine	27 (7)	29 (8)	39 (11)
Lysine	148 (40)	152 (71)	198 (74)

Analysis of variance $p<0.05$

For these three amino acids, babies fed Preaptamil had the highest and babies fed SMA–LBW the lowest concentrations.

Therefore we feel Ventura and Brooke were wrong to group together all amino acid results on babies fed different formulas as the type of formula may determine amino acid concentration.

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Drs Ventura and Brooke comment:

We thank Dr Bell and her colleagues for their comments We were unaware of their paper when we submitted ours. There may well be differences in plasma amino acids depending on the type of preterm formula used, just as there will be differences if one formula is fed at different volumes.

The purpose of our paper was not to compare formulas—only two infants were fed on formulas other than SMA Low Birthweight—but to examine the effects of a relatively high protein intake (in comparison with, for example, banked breast milk) in very low birthweight infants The infants in our study were appreciably smaller than those studied by Bell and her colleagues, but even so no potentially hazardous amino acid concentrations were detected

Nebuhaler in young asthmatic children

Sir,

We read the article by Pool *et al*[1] with special interest because inhaled bronchodilators are underused in French asthmatic children.

Bronchodilator repsonsiveness is reliably assessed in a pressure-type body plethysmograph (Fenyves and Gut, Basel) allowing the measurement of specific airway resistance (SRaw) even in young children Indeed this method does not demand active cooperation.[2] To measure the efficacy of the Nebuhaler we studied 21 asthmatic children (mean age 5 5 years, range 3–8) They were randomly assigned to either metered-dose inhaler (group A, n=9) or Nebuhaler (group B, n=12). Each child was given two consecutive puffs of terbutaline (500 μ) according to Reiser and Warner's technique for metered-dose inhaler[3] and that of Pool *et al* for the Nebuhaler [1]

Basal SRaw (mean (SD)) was similar in group A (14·4(8·9) cm H_2O/l/second) and B (14·2 (5 8) cm H_2O/l/second) Fifteen minutes after inhalation SRaw decreased, but not significantly in group A (9·3 (4·3) In contrast in group B (Nebuhaler) the decrease in SRaw was highly significant (6 9 (2 3), $p<0{\cdot}01$, Student's *t* test and Wilcoxon).

Although the numbers were small these results support the idea that in young children (≤8 years) even closely medically supervised, hand-lung coordination is poor and/or unpredictable whereas pear shaped spacers are efficient and merit a wider usage However in children aged >8 years, properly instructed, metered dose inhalers were shown to be as effective and more practical than spacer devices (results not shown)

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Disposable nappies—a cautionary tale

Sir,

Recently a mother brought one of her sons (aged 2 years) to casualty having discovered an unusual orange/brown jelly like material in his nappy. The material was shaped like a flattened ovoid with an irregular surface, some 20 mm in diameter at the broadest point and 12 mm in width. On examination, the child was found to be normal and the material sent to the laboratory for analysis.

On first examination the material resembled faeces but was a resiliant jelly like material which did not smear easily on a microscope slide (unlike faeces) and did not take any stains for fat or protein It was also resistant to common solvents such as water, dilute acids and alkali, ethanol, and ether

A clean disposable nappy was obtained and cut in two. The cotton wool was found to be impregnated with a crystalline powder which absorbed water readily, forming a clear gelatinous mass Use of coloured solutions resulted in the jelly retaining the colour, and urine produced a substance remarkably like the original material found in the child's nappy

The advent of 'stay dry' nappies where the water from urine is absorbed and retained has been heralded as a new development, contributing to the prevention of 'nappy rash' In this case, the mother had purchased a batch of nappies that were being marketed as rejects It is likely that an inherent defect in them, plus the child being left unchanged for some time, lead to the appearance of the gel.

Work by one of the manufacturers of such nappies has shown that the polyacrylate gel used to retain the water is non-toxic and is unlikely to harm the child As we have now had several such cases, we wish to draw your readers' attention to the matter so that mothers who encounter the same situation may be reassured that the unusual nappy contents have not come from the child.

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Percussion as an aid to suprapubic bladder aspiration

Sir,

I read with interest the article by O'Callaghan and McDougall showing the value of checking for the presence of urine in the bladder by ultrasound before attempting suprapubic bladder aspiration.[1] Not having the benefit of ultrasound for this purpose I have found gentle percussion very helpful. I palpate the symphysis pubis and then start below the umbilicus and percuss gently from above downwards. As Nelson and Peters state,[2] the neonate's bladder extends above the symphysis pubis as it fills. If I encounter bladder dullness one to two fingerbreadths above the symphysis, then aspiration is worth attempting; otherwise not. The percussion should be gentle because vigorous percussion might stimulate the bladder to void.

Another pitfall to avoid is placing the needle too close to the symphysis pubis and directing it down into the pelvis, which results in the needle going below the bladder. With the baby supine, Nelson and Peters insert the needle 2 cm above the symphysis and angle it only 10–20° from the perpendicular.[2] I find that if a nurse holds the legs and trunk firmly down on the couch (or bed) then that tilts the pelvis forward slightly and I hold the needle perpendicular.

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Ranitidine in the newborn

Sir,

The report of Rosenthal and Miller describing the use of ranitidine in the newborn[1] prompts us to draw attention to a complication of the use of cimetidine, the most commonly available H_2 antagonist in an intravenous form.

A baby boy, delivered in good condition at 36 weeks' gestation and weighing 650 g developed bilateral intraventricular haemorrhages, with normal coagulation, within the first 24 hours of life. Apnoeas ensued and penicillin and gentamycin were commenced, and he was mechanically ventilated for 36 hours. Upper gastrointestinal bleeding occurred on the fourth day and cimetidine in a dose of 20 mg/kg/day was commenced in four divided intravenous doses. Bleeding was noted from puncture sites after the seventh dose. Platelet count had fallen from $117\times10^9/l$, 36 hours previously, to $22\times10^9/l$ with normal coagulation studies. Platelet count rose to normal within four days of stopping the medication. The posthaemorrhagic hydrocephalus which developed became stable and no further episodes of thrombocytopenia or bleeding occurred.

Thrombocytopenia has been reported in a number of adults, and the increased use of H_2 antagonists in neonates means that users should be aware of hazardous side effects of drugs previously rarely used in this age group.

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Neonatal infection and human immunoglobulin

Sir,

I read with interest the paper by Conway and his colleagues.[1] It is unfair to say that 'there are few studies on the use of immunoglobulin preparations in premature babies and their conclusions are equivocal' when the authors do not refer to the pioneering work of Professor Sidiropolous, who has clearly shown the beneficial effects of intravenous immunoglobulin (IVIG) in the treatment of neonatal sepsis,[2] and ourselves, who have shown the effect of IVIG in the prevention of neonatal sepsis.[3]

We are not quite sure how many injections and of what volume were given to each infant. It is not surprising that the concentrations of serum IgG achieved were below that of the term infant. The absorption and bioavailability of the intramuscular preparation and the local blood supply could be responsible. In the study by Sidiropolous and ourselves using IVIG we could achieve serum IgG concentrations greater than those seen in the term infants.[2] [3] We also cannot see the justification of giving weekly painful and costly injections to these very tiny infants with very little muscle mass when similar results have been shown previously by us using a single intravenous injection.

It is not entirely possible to exclude nursing bias in favour of not reporting the 'soft signs' of sepsis in infants who were receiving immunoglobulin treatment as the control group did not receive a similar placebo injection.

It would be interesting to known if the author measured serum IgM concentrations as we found them to be increased after IVIG.

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Dr Conway comments:

I am pleased to read of Dr Haque's interest in our paper and apologise for not referring to his work, of which I am aware None the less, I think it is difficult to extrapolate from his population to ours, for reasons I have already outlined.[1]

Dr Haque, in reference to our work, questions the 'justification of giving weekly painful and costly injections'. At the time of the conception and early stages of our study, intravenous immunoglobulin preparations had not received full product licencing in this country. May I remind Dr Haque that our study was approved by the hospital ethical committee and that we would not have given these infants intramuscular injections except as a logical extension of our previous work[2] and in reasonable expectation of their being of benefit to the child The cost of prophylactic immunoglobulin treatment, if successful, is more than offset by the saving in expensive antibiotic use

I absolutely refute Dr Haque's suggestion of possible nursing bias The substantiation of a doctor's academic hypothesis weighs little with our intensive care nurses compared with the continued well being of their patients Moreover, in a busy regional unit with much active research in progress, every nurse was not necessarily always aware of which baby was, or was not, receiving immunoglobulin treatment.

The preparation used contained 250 mg in 1·7 ml and volumes injected were therefore small. As stated, injections were at weekly intervals until discharge to home We were also not surprised that the concentrations of serum IgG were below those of term infants, for reasons similar to those described by Dr Haque We did not measure IgM concentrations

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When is meconium stained liquor actually bile stained vomit?

Sir,

In a recent issue of the *Archives*, Griffiths and Burge report three cases of what was initially assumed to be meconium stained liquor but which was actually a manifestation of intrauterine bilious vomiting [1] They point out that insertion of a thermometer into the rectum, or at least an attempt to do so, would alert people to the possibility of intestinal obstruction resulting in apparent meconium staining of the liquor.

I have seen two neonates, who turned out to have intestinal obstruction, who presented with what was thought to be meconium staining of the liquor. Gastric aspiration in the labour ward produced in excess of 50 ml, and in one case 150 ml, of green liquid I would therefore like to point out that if meconium staining of the liquor is thought to warrant a laryngoscopy with or without the insertion of an endotracheal tube it is reasonable also to pass a nasogastric tube and if large volumes of green liquid are obtained from the stomach this suggests that the problem is intestinal obstruction and not in utero passage of meconium

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Facts for teachers of children with cancer

Sir,

The valuable paper by Dr Stevens and colleagues raises important issues [1]

(1) Teachers should be more informed in a general sense, in as much detail as they themselves would find helpful, about conditions such as malignant disease, cystic fibrosis, and diabetes (the most obvious examples) which can have a pervasive effect on the well being of children in school.

(2) As an important general rule (to which there may be exceptions in individual circumstances), teachers should not be given medical details about individual children The confidentiality aspects of passing on such information cannot be controlled in mainstream or even special schools in the way which is presumably practicable in the context of teachers' work in the health services dominated environment of a hospital

Doctors who do not work regularly in schools may be unaware of the extent to which educational records are increasingly 'open', with corresponding availability to staff of any medical information in writing which goes to the school, and the encouragement of informal exchanges of information Medical matters tend to fascinate large numbers of the non-medical public, including professionals, and we can neither expect nor monitor an adequate level of respect for the confidentiality of certain information in non-medical environments such as schools A 13 year old girl with advanced malignant disease was quoted recently on television as saying that 'everybody' at her school knew about her condition and its implications, and that this single circumstance caused her more misery than anything else

(3) Dr Stevens *et al* quote the British Paediatric Association *Report on the school health services,*[2] but do not directly mention the school health service In my view a relevant school health service could and should make it its business to provide appropriate support and advice to schools and individual teachers as necessary about individual children, which implies close links between

regional oncology centres and the school health services in the surrounding health districts. Only in this way can schools and individual teachers be given appropriate support, which includes adequate confidentiality safeguards

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Glycosylated haemoglobin and cystic fibrosis

Sir,

Fluckiger recently reported interference in glycosylated haemoglobin A$_1$ (HbA$_1$) estimation by penicilloylated haemoglobin.[1] He concludes that measurements of HbA$_1$ can be misleading in patients with cystic fibrosis receiving treatment with penicillins because of covalent binding of the penicilloyl moiety to haemoglobin producing HbA$_1$ mobility of the respective haemoglobins. Raised HbA$_1$ concentrations were found in patients with cystic fibrosis treated with long term β lactam antibiotics who did not have diabetes Lower HbA$_1$ concentrations were obtained on converting thiobarbituric acid values to the HbA$_1$ equivalent for comparison. Although it is stated that the patients with cystic fibrosis did not have diabetes, it is not reported whether glucose tolerance tests were completed to determine if there was impaired glucose tolerance in these patients.

We studied 64 patients with cystic fibrosis measuring HbA$_1$ by ion exchange column chromatography and spectrophotometry (Biorad haemoglobin A$_1$ by column test) expressed as a percentage of the total haemoglobin. Our laboratory reference range is 5·3–8 8% representing 2 SD limits of the mean in normal paediatric departments. Forty three patients with cystic fibrosis had a mean (SD) HbA$_1$ concentration of 7·8 (0 9)%, range 5·9–8·8. This was not statistically different from the mean HbA$_1$ concentration of [illegible] (0·94)% of 21 normal children admitted for routine operations All the patients with cystic fibrosis were on long term antibiotic prophylaxis mainly with β lactam antibiotics HbA$_1$ concentrations were obtained on each of the 43 patients with cystic fibrosis on one to four occasions. There was no statistical difference between the mean HbA$_1$ concentration of 7·6 (0·9)% (n=43) of the patients treated with flucloxacillin for at least a two to three month period before estimation and the mean HbA$_1$ concentration of 7·7 (0·8)% (n=24) for patients on both flucloxacillin and ampicillin These did not differ from the HbA$_1$ concentrations of the control population. We found evidence of impaired β cell function in patients with raised HbA$_1$ concentrations by measurement of C peptide concentrations during oral glucose tolerance test [2]

Thus there was no evidence from our study that β lactam antibodies produce falsely raised HbA$_1$ concentrations using the Biorad method. Although Fluckiger reports a potential problem, the evidence that it should deter the measurement of HbA$_1$ in patients with cystic fibrosis other than by specific techniques is lacking

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ook reviews

**reening for Hearing Impairment in
ung Children.** By B McCormick.
110· £8·95 paperback. Croom Helm,
38 ISBN 0–7099–4643–0

is book concentrates on the methods of
eening hearing of children between the
es of 6 months and 3·5 years of age
ere is a very brief section on the concept
actual hearing screening but most of the
ok is directed to the practical aspects of
screening procedure There are sec-
ns on the choice of stimuli used, the
of a sound level meter to measure
muli, and on the actual technique for
ting of babies with mental ages of 6–18
nths, 18 months–2·5 years, and 2 5
ars–3·5 years For the older children
re is also a discussion of suitable speech
crimination material and the author
ncentrates throughout on the test and
ocedures that have been developed in
ttingham There is also a chapter cover-
acoustics, hearing, and causes of deaf-
ss, but medical readers would find this
ched at too basic a level The final short
apter covers screening techniques that
being evaluated at the moment These
really geared to the neonatal popula-
n and would be interesting for profes-
nals not directly involved in the field
o have gained some insight into present
lds of investigation

Overall this book would be of interest
inly to doctors and other professionals
o are concerned with preschool hearing
eening. The importance of the book lies
the very strong emphasis on accurate
d reliable screening techniques with very
ar instructions as to how the tests should
carried out This is very important if
untrywise we are to improve our present
adequate hearing screening programmes

S BELLMAN

**rns in Children: Pediatric Burn Manage-
nt.** Edited by HF Carvajal and DH
rks Pp 385. £56 hardback Year Book
edical Publishers, 1988 ISBN 0–8151–
42–7.

is book provides as comprehensive a
xtbook on the subject as is available at
is time, albeit from a distinctly trans-
lantic perspective The opening section on epidemiology and burn prevention in childhood is a major area of concern given the current magnitude of the problem of burns in children Controversies in fluid resuscitation are reviewed in excessive detail with a somewhat unhelpful conclusion. The ensuing chapters contain much more practical management plans for resuscitation, dressing, antibacterial treatment, and nutrition, together with common pitfalls clearly outlined; this is valuable material for anyone getting to grips with burns management. Surgical treatment options are well described, and the chapters on wound cover and dressings are admirably up to date Two further lengthy sections are devoted to infection, immunology, and organ failure.

The book ends with four excellent chapters on rehabilitation, the first on hypertrophic scarring is a succinct review of this controversial subject, which unfortunately does not deal with the changes induced by the various treatments which are currently available. The occupational therapist's role is well described, as are the readable descriptions of psychosocial care and discharge planning, which are so often given perfunctory consideration by attending surgeons. A short final chapter devoted entirely to discharge planning indicates the importance this subject is given in the editors' units

This is a well planned book which should prove a useful reference volume for burns units For the junior doctor learning burns management it may prove too detailed and indigestible unless a special interest is to be developed The historical background passages and reference lists are comprehensive and very valuable More than a little of the book is directed at burns in all age groups, and it occasionally lacks the specific paediatric concern which singles it out from the many other general burns texts

T E E GOODACRE

L'Enfant et Sa Santé: Aspects Epidemiologiques, Biologiques, Psychologiques et Sociaux. Edited by M Manciaux, S Lebovici, O Jeanneret, EA Sand, and S Tomkiewicz Pp 1326, UK price unstated. Doin Editeurs, Paris, 1987 ISBN 2–7040–0539–7

In this ambitious multiauthor text a large number of contributors who are almost entirely from French speaking countries —especially France, Switzerland, and Belgium—have summarised information concerning the physical, social, and psychological development of the child Evidently a public health approach to paediatric disorders and paediatric epidemiology is thriving in these countries as the abundant references to unfamiliar studies published in French journals made this reviewer, at least, feel inadequately parochial in his knowledge There are especially good sections on the Sudden Infant Death Syndrome and on accidents and accident prevention The book will be found a valuable source of information by anyone seeking an up to date account of French social paediatrics

P J GRAHAM

Childhood Pain. By D M Ross and S A Ross Pp 384 £39·50 hardback Urban and Schwarzenberg, 1987 ISBN 0–8067-1631-2.

A friend recently made a comment which surprised me at the time, suggesting that American thought is much more Teutonic than British, but this book illustrates that point. In a wealth of detail, it presents information about the history of our understanding of pain, methods for evaluating, managing, or preventing pain, with carefully documented references throughout, which ultimately constitute 12·3% of the total pages This attention to detail which is its mark, as well as its intended interdisciplinary readership, make it rather difficult for the clinician to do more than learn from and perhaps build upon other peoples' research There are, however, useful chapters, particularly an early one dealing with the child's view of pain in different age groups and a later one on behavioural and cognitive intervention before painful procedures and during pain

Pain is seen to stem from a mix of factors which can be difficult to untangle. thus emotional and physical pain enhance each other. Kinds of pain discussed range from the acute pain (of dressing burns or of bone marrow aspiration) to chronic or recurrent pain (rheumatoid disease, migraine) and there is a welcome emphasis on helping the child to cope with such discomfort. It has to be said that the chapter on the physical management of pain, with its emphasis on a pharmacopoeia largely unfamiliar to British paediatricians, is less help than other sections that deal with behavioural and cognitive intervention, providing as they do ideas for play therapists and psychological strategies for children to use. Those of us who have a sinking feeling that there should be a greater use of these strategies in both medical and surgical children's wards may be comforted that in one of the authors' own research projects, which asked what would help a child most when experiencing the 'worst pain ever', 99·2% of the children felt that, regardless of the kind of pain, the 'thing that helped most' was to have one or both parents present. Here, at least, we are on home ground.

J GOODALL

Pediatric Surgical Pathology. 2nd ed. By L Dehner Pp 1121. £147 hardback. Williams and Wilkins, 1987. ISBN 0-683-02425-6.

It is rare that a reviewer of my degree of senility handles a book that can be recommended without reservation. This is one such.

Every clinical paediatric pathologist will be familiar with the first edition of *Pediatric Surgical Pathology,* which appeared over 0 years ago, and will have wondered about a new edition. This book is about twice the size of the first (3·5 kg) with over 1100 pages and firmly packed three column script, and an almost similar number of photographs. Louis Dehner has involved some others to help him in some sections of the book but most of the writing appears to be his alone The term 'surgical pathology' is perhaps a too limiting term for this book's scope which covers virtually every organ and tissue In the renal tract, renal biopsies and metabolic disease receive as much attention as cysts and gross anatomical 'surgical' deformities. The book covers all of the medical conditions for which the biopsy needle can be applied. It is difficult to find a section of this book that has less than 1000 references, the kidney itself has about 1400, and every section list contains many in 1986, within a year of th date of publication.

This is a black and white book The have been a number of recent colo atlases of children's pathology, whic against this look like popular coffee tabl volumes and beside this volume look slic and superficial—which they are! The m crophotographs are of good quality an there is a scattering of reproductions clinical radiographs that will help the clin cian If I have one criticism, it is that th reproduction from gross specimens hav that slight woolly texture that suggests th they have been obtained from colo slides

This book costs £147 but its value relate to the extent of its contents is cheap. I scope is encyclopaedic, its style concise an non-philosophical—it is a very practic workbook. It is a high priority book f inclusion in any paediatric department library, an essential book for departments paediatric pathology, and a reference boo for general departments of pathology

J L EME

29.11.90

Vol 63 No 9 September 1988

ARCHIVES OF DISEASE IN CHILDHOOD

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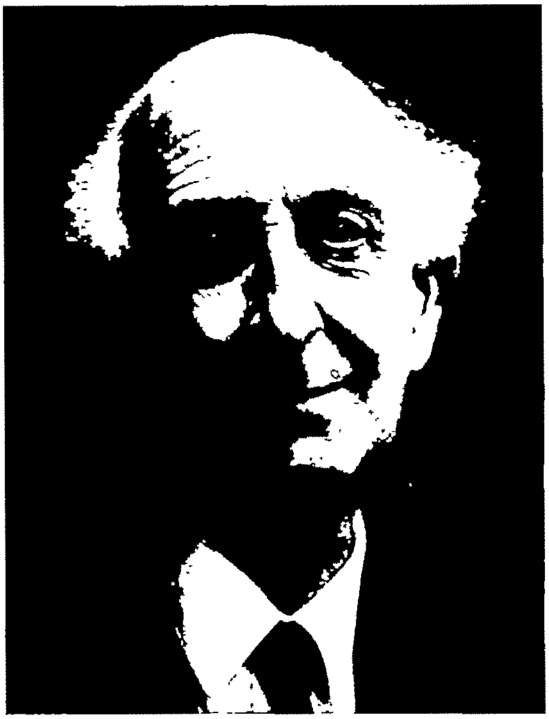
James Spence Medallist, 1988

Professor Otto Wolff

The James Spence Medal was presented to Professor Otto Wolff on 13 April 1988. Professor John Forfar, President of the British Paediatric Association, gave the following citation:



Professor Otto Wolff

When formally asked to record his profession Otto Wolff does not do so in academic or scientific terms but merely writes 'paediatrician'. That has always been his primary aim—to be a good doctor of children—and in achieving that aim he has surely been immensely successful. A letter written to him in appreciation of a period he had spent in another university centre as visiting professor exemplified so much of Otto the paediatrician It said 'We shall always remember your extreme courtesy to the children which was an example to us all'.

Qualifying in Cambridge in 1943 Otto became Lecturer in the Department of Child Health in Birmingham in 1951, remaining there for 14 years and finishing as Reader under the late Professor Sir Douglas Hubble. In 1965 he was appointed to succeed Sir Alan Moncrieff as Nuffield Professor at the Institute of Child Health in the University of London and occupied that leading position in paediatrics for 20 years.

In research Otto has made his mark in several fields. His first paper to the BPA was on meningitis. The problem of childhood obesity had been little researched when his interest in it was aroused. It formed the subject of his MD thesis and has remained an important interest of his throughout his career He was probably the first paediatrician in Britain to set up a clinic for obese children.

From obesity he turned to the study of plasma lipids. With Harold Salt as his biochemical partner, he pioneered the techniques of lipoprotein electrophoresis establishing the value of this even before the Frederickson classification was announced. He also explored the role of lipid disturbance in childhood as a precursor of coronary artery disease and his recognition in 1960 of the rare condition of abetalipoproteinaemia led to important work on vitamin E metabolism.

Inheriting a large clinic of children with phenylketonuria from his predecessor at Great Ormond Street and later becoming Chairman of the MRC/DHSS PKU Register Otto guided much of the research which emanated from that Register. His coordinating role enabled the group which he headed to establish management principles for PKU and to show how successful treatment could be. The need for long term follow up which characterised this work was a principle which he also successfully promoted in other fields

The studies on PKU and plasma lipoproteins exemplified much of Otto's ability to influence and inspire others and, when they showed academic aptitude or inclination, to support them in their research. He also recognised the importance of developing specialised units in a centre such as Great Ormond Street and the outstanding work done there in the fields of gastroenterology, metabolic disease, and tropical paediatrics was the direct result of his initiatives.

Otto is perhaps at his happiest when dealing with patients. Those who have worked closest with him recognise what a superb clinician he is and how good at talking with children and parents From his earliest days he has seen the need to involve himself in the emotional as well as the physical aspects of childhood problems and he has enjoyed the closest collaboration with child psychiatrists and psychologists.

Whether among undergraduates in Birmingham or postgraduates in London Otto believes in teaching by example. His emphasis is on how to take a history, deal with parents and children, and use the literature. Regarding the latter one of his junior colleagues was heard to comment, 'We have to move fast if we are to get the appropriate reference before the Professor'.

Some professors are men of culture, many traditionally have their idiosyncrasies. Otto matches up to both of these professorial criteria. His culture is the culture of the musician and he is a dedicated pianist. Wherever he goes he either seeks out a piano or a group of enquiring men struggling with a piano are seen seeking Otto. He and his wife Jill are excellent hosts but those who have travelled with Otto have learned that his hospitality is not confined to his home. Be it the early hours of the morning in some foreign part or at the nadir of blood sugar on a long British Railways journey Otto can be relied upon to produce a flask of coffee and to unwrap that Otto Wolff specialty, the marmalade sandwich.

Otto has chaired many important committees. Unsought, and by him unexpected, many honours have come his way. He has been the President of the British Paediatric Association, he was awarded the Dawson Williams Prize of the BMA, the Harding award by Action Research for the Crippled Child, and the medal of the Association Française pour la Dépistage et la Prévention des Maladies Métaboliques et des Handicaps de l'Enfant. He has been made an honorary member of numerous foreign paediatric associations. He was created CBE in 1985

In honour of one who has amply fulfilled the criteria for the Spence Medal by his outstanding contributions to the advancement and clarification of paediatric knowledge the British Paediatric Association presents to Otto Wolff its highest award, the Spence Medal.

James Spence Medallists

1960	Professor A A Moncrieff
1961	Professor R A McCance
1963	Sir F Macfarlane Burnet
1964	Professor L S Penrose
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Archives of Disease in Childhood, 1988, **63,** 1005–1006

Annotations

Diagnostic radiography in children

The Japanese survivors of the atomic bombs are the largest group of people to be exposed to substantial doses of ionising radiation. They have been subjected to careful medical follow up that is continuing, and it is on the reports about these people that we chiefly depend in assessing the risk of cancer from ionising radiation.[1] New estimates of the doses of radiation that they received, and the realisation that excess cancers are still appearing 40 years after the exposure, has led to substantial increases in our perception of the risks of ionising radiation.[2] This increase in the perceived risks is most obvious with children, and this must lead to a reassessment of the hazards of paediatric diagnostic imaging by ionising radiation.

The units used to measure ionising radiation are the Gray (Gy), which is the dose absorbed by an organ, and the Sievert (Sv), the effective dose equivalent, which takes the dose absorbed by each organ and weights it according to the sensitivity of that organ to a lethal cancer or to the induction of serious genetic injury. The dose of radiation to a population is measured in man Sv and is the sum of the individual doses in Sv. The dose to the gonads is measured in Gy.

The harm that one man Sv causes used to be assessed at a 1% chance of developing a lethal cancer/man Sv,[3] and there was an indication by an influential committee that the hazard was less than this in the young.[4] New data are available concerning the risk of excess lethal cancer for children exposed to the atom bombs.[2] Full interpretation of these data is awaited, but a possible risk of lethal cancer in children is 5%/Sv in boys, and 9%/Sv in girls. Table 1 is based on these risk factors. The considerably larger risk in girls is because the young girl's breast is extremely sensitive to radiogenic cancer. The new Japanese reports have not altered our perception of the magnitude of the genetic injury, which is based on animal and in vitro studies. Assuming an expectation of 1·6 offspring/child, the risk of serious genetic ill health within the first two generations is assessed at 1·6%/Gy.[5]

The dose of radiation received by a child during an *x* ray examination varies depending particularly on the child's size and on the nature of the examination. Table 1 shows possible dosages for large and small children together with the number of examinations required to cause a lethal cancer. Note that the radiation dose from examination of a peripheral limb (for example, wrist or knee) is minute. Even an adult is likely to receive as high a dose from natural background radiation while the patient is in the department as from the examination. Table 2 gives possible doses to the gonads and the subsequent risks. These should be regarded as mean figures; variations in doses given to patients as large as tenfold have been reported between hospitals.

It will be noted that the doses for neonatal examinations are usually small. A neonate living in an area of low background radiation (such as

Table 1 *Risk of lethal cancer after diagnostic radiography*

Examination	*Approximate dose of radiation (mSv)*	*Examinations/lethal cancer*	
		Male patient	*Female patient*
Small neonate:			
Chest	0·01	2×10^6	$1{\cdot}1\times10^6$
Contrast meal	0·1	2×10^5	$1{\cdot}1\times10^5$
Large teenager:*			
Chest	0·05	4×10^5	$2{\cdot}2\times10^5$
Barium meal	3·83	5000	3000
Lumbar spine	2·15	9000	5000
Thoracic spine	0·92	22 000	12 000

*Adult doses of radiation.[6]

Table 2 *Risk of genetic injury after diagnostic radiography*

Examination	*Approximate dose of radiation (mGy)*		*Examinations/ serious genetic injury*	
	Male patient	*Female patient*	*Male patient*	*Female patient*
Neonatal:				
Chest	0·001	0·001	6×10^7	6×10^7
Abdomen	0·04	0·03	$1{\cdot}5\times10^6$	2×10^6
Large teenager:*				
Chest	0·0025	0·002	$2{\cdot}5\times10^7$	3×10^7
Abdomen	1·6	0·8	40 000	80 000
Barium enema	3·4	16	18 000	4000

*Adult doses of radiation.[7]

London or Manchester) would have to have 50 chest *x* ray examinations before the ionising radiation he received before his first birthday exceeded the radiation received by a child who had had no chest *x* ray examinations but lived in an area with high background radiation (such as Cornwall or Aberdeen). On the other hand the doses for the large teenagers are substantial, and the risks correspondingly high.

The doses of radiation from isotope examinations are also variable, depending especially on the type of examination. As the activity of the dose given in nuclear medical imaging is usually proportional to the patient's weight, the effective dose equivalent in children and adults is likely to be more similar than in *x* ray diagnosis. Examples of possible doses are: ^{99m}Tc brain scan 5·5 mSv, and renogram 0·2–0·4 mSv.[8]

Radiation received by staff on a neonatal unit is generally negligible. If a newborn baby is held during a radiographic examination with the hand outside the primary beam, a million babies a year may be held by one person without the dose to the hand exceeding the dose limit allowed in industry. Even with the hand in the primary beam, 25 000 exposures a year would be allowed. Somebody standing, with no lead protection, three metres from a neonate having a chest *x* ray examination will receive about 0·00002 µSv; this is about the same as the extra radiation received by spending one second in Cornwall rather than in Manchester. Exposure of staff to radiation during more complex procedures such as cardiac catheterisation is much greater, and there must be rigorous methods of protection.

The risk to a neonate from the radiation used in radiography is negligible. If there is a proper clinical indication for the examination there need be no hesitation in carrying it out. It is quite different in larger children, and the new perception of the risks in this group will lead to the avoidance of ionising radiation for other than the low dose examinations. Ultrasound and magnetic resonance imaging should be used where possible, and alternative techniques of diagnosis (such as endoscopy) must be encouraged.

The search for ways of lowering the doses of radiation is important. An antiscatter grid is unnecessary for fluoroscopy of neonates, and eschewing it will halve the radiation dose.[9] Rare earth screens should always be used for children, and indeed adults, and at least halve the dose compared with simple tungstate screens.[10] The use of carbon fibre material in certain components also causes a reduction in dose that can be as much as a further halving.[11] Radiologists should ensure that these methods of reducing radiation are used in their departments.

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Intraspinal tumours

Spinal cord tumours in children are rare—they occur between five and 10 times less commonly than intracranial neoplasms.[1 2] The general paediatrician is likely to encounter only one or two children with this condition in a whole lifetime of practice. Presenting symptoms are often vague and it is thus not surprising that these tumours are frequently misdiagnosed. It is not unusual for the interval between presentation and accurate diagnosis to be as long as two or three years.

About 70% of intraspinal tumours in children are benign and slowly growing, with symptoms evolving in a subtle fashion. Nevertheless neurological dysfunction due to cord compression is an ever present danger and the prognosis for neurological recovery is poor once a severe deficit becomes established. Acute spinal cord compression, usually due to an ischaemic insult, may result in a precipitate loss of neurological function below the level of the lesion and even when treated promptly significant recovery may not occur.

Pathological features

The presenting clinical features depend on the cord level of the lesion and also whether the tumour is extradural, intradural but extramedullary, or intramedullary. As a rule of thumb, 40% of intraspinal tumours occur in the thoracic region with the remainder being evenly distributed between the cervical and lumbosacral segments. Extradural tumours (for example, neuroblastoma and sarcoma) account for almost half of intraspinal tumours in childhood, spreading from nearby bone or through intervertebral foramina. Intradural but extramedullary tumours occur in one quarter of patients, the commonest lesions being neurofibromata, dermoids, and lipomata. More than a quarter of all intraspinal tumours in childhood are intramedullary (a significantly higher proportion than in adults) and most of these are slowly growing astrocytomas. Many astrocytomas are relatively well localised but sometimes there is extensive involvement of the cord from the lower brainstem or upper cervical region to the conus. These 'holocord' astrocytomas are associated with large cystic dilations throughout the cord.[3]

Clinical presentation

Boys are a little more often affected than girls. The highest age specific incidence is found in infancy due to the predilection of neuroblastoma and congenital tumours to present at this time, but no age is exempt.[1]

The commonest manifestation of intraspinal tumour in childhood is motor weakness (spastic or flaccid depending on cord level). In the young infant the parents may observe failure or reluctance to move one or both legs, while there may be delay in walking or unwillingness to stand in the toddler. In the school age child progressive motor weakness is often heralded by a limp or other gait disturbance. Occasionally these symptoms are accompanied by segmental muscle wasting.

Back or root pain occurs in at least 40% of children with intraspinal neoplasm but it is a much less common presenting sign in children than in adults. Spinal pain is most often dull and aching in quality and localised to dermatomes adjacent to the tumour. Root pain, which is less frequent, is usually projected over a single dermatome and it is unclear whether this is caused by swelling of the spinal cord with distension of the root, or whether the root entry zone is infiltrated with tumour. Often the site of pain may suggest other more common clinical entities, particularly acute intra-abdominal disease when lower thoracic nerve roots are involved. The child under 4 years will be unable to describe or to localise accurately his discomfort, while in the infant pain must be inferred from irritability.

With slowly growing tumours, neuromuscular imbalance and growth may produce musculoskeletal deformity such as head tilt, torticollis, kyphosis, or scoliosis. Such deformity is commonly accompanied by pain, especially night pain. In any child who presents with a progressive musculoskeletal deformity, even in the absence of neurological deficit, intraspinal tumour must be considered.[4 5]

Various degrees of bladder and bowel dysfunction and other sensory disturbances are present in about 30% of children at the time of presentation. A history of delayed development of sphincter control is suspicious, but even more significant is a change in bladder or bowel habit in the previously continent child. One of the major pitfalls in diagnosis is the failure to appreciate the significance of more trivial symptoms such as constipation, anal pain, or secondary enuresis in the child presenting with limp, backache, or leg pain. The symptoms of a patient suffering from intraspinal tumour are often exacerbated by coughing, crying, or straining. Occasionally symptoms are first highlighted by trauma and sometimes these may misleadingly diminish or even disappear, only to recur more insidiously later.

Under exceptional circumstances, intraspinal tumours may present as hydrocephalus, most likely due to raised protein concentrations causing defective absorption of cerebrospinal fluid. Intraspinal dermoid tumours may present as recurrent meningitis if there is a direct extension from the skin surface.

Neurological examination may show a plethora of abnormal signs or no abnormality. Upper motor neurone findings may be less well defined than lower motor neurone findings, the latter signs generally offering a better indication of the level of the lesion, unless the abdominal reflexes are involved. Local tenderness over one of the spinous processes may also suggest a level. Detailed sensory examination is obviously of limited value in the very young patient but some idea of the presence or absence of perianal anaesthesia and pinprick levels can usually be obtained even in infants. Inspection of the skin may suggest neurofibromatosis whereas hepatomegaly provides a clinical clue in neuroblastoma.

Investigation

Plain radiographs of the entire spine (anteroposterior and lateral views) should be carried out as they often show bony abnormalities and strengthen clinical suspicions.[6] There is no place for routine lumbar puncture in the management of the child. Although examination of the cerebrospinal fluid may be useful for demonstrating a raised protein content or the presence of tumour cells, this advantage is greatly outweighed by the potential hazards of the procedure. Lumbar puncture may lead to further cord damage at the site of compression, particularly in cases of spinal block where tumour has obstructed the cerebrospinal fluid circulation and removal of fluid below the lesion leads to downward displacement of the cord and tumour. Ill considered lumbar puncture may also delay successful myelography for several days.

Further investigation of the child should be undertaken by a paediatric neurologist at a neurosurgical centre. Computed tomography of the spine and in particular magnetic resonance imaging of the spinal cord are relatively new imaging techniques which may rapidly confirm the presence of an intraspinal mass.[7, 8] High resolution computed tomography with intrathecal contrast enhancement is a valuable but nevertheless invasive procedure and several studies have shown the superiority of magnetic resonance imaging in diagnosing spinal cord tumours in children.[8, 9] Magnetic resonance imaging is a non-invasive method of providing high resolution images which differentiate not only between cystic and solid tumour areas but also between tumour and surrounding oedema.

In most centres myelography remains the definitive investigation. In the presence of an intraspinal mass, myelography itself sometimes leads to rapid deterioration in neurological function. The investigation should thus be regarded as an integral part of the neurosurgical procedure, carried out with the full knowledge and availability of the neurosurgeon. The opportunity for examination of the cerebrospinal fluid should be taken at this time. In very few patients will myelography precipitate urgent exploratory laminectomy and surgery may be safely deferred for several days in most children.

The treatment of the tumour depends on the site and histological diagnosis of the lesion. Advances in microsurgical techniques including the use of the ultrasonic aspirator (Cavitron) and carbon dioxide and argon lasers, along with refinements in radiotherapy have led to a greatly improved outlook, especially in intramedullary tumours.[3, 10, 11]

It is clear that early recognition of these rare tumours is important, as their effects are often devastating whereas prompt surgical intervention may produce very favourable results. Although new non-invasive imaging techniques promote swift and sometimes precise definition of such lesions, there is little doubt that a high index of suspicion remains our most valuable diagnostic tool.

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The aftermath of Cleveland

The sexual abuse of children so offends the social taboos of society that its discovery provokes strong reactions and polarisation of opinion among the public, politicians, police, and the professions. Family studies have shown that such abuse may span five generations and investigation of 'index' cases has revealed the appalling activities of child sex rings. So protean have been the overt manifestations, so secret the activities, that doctors in all branches of the profession, who treat children, have often failed to recognise the problem. We are in the 1980s at about the same state of knowledge of sexual abuse as we were in the 1960s as regards to the physical abuse of children. Then and now, extravagant claims have been made about the incidence of the abuse.

For those professionals who have become involved in trying to tackle the complex problems in the presence of the apparent professional apathy, determination and enthusiasm to put the needs of the children first has been interpreted as excess zeal: while those of us who have failed to recognise sexual abuse in the past have reacted defensively and sometimes with hostile disbelief. In these circumstances balanced professional judgments for recognition of sexual abuse are made more difficult.

Many manifestations of sexual abuse are covert, but much more difficult to recognise than physical abuse. This often has overt, more distinct and now well recognised patterns of bruising with definite radiological appearances. Professional reaction to physical abuse has become relatively standardised throughout the country, but the catalogue of 34 child abuse inquiries in this country bears witness that its management is fraught with human error and procedural difficulties. It was the rigid application of such procedures to the problem of child sexual abuse that provoked the crisis in Cleveland, which gave rise to the inquiry by Lord Justice Butler-Sloss, published in July this year.[1]

Childrens' wards with paediatrically trained staff and an appropriate environment should be the proper place for children to be examined in an understanding and non-threatening way. Childrens' wards should also be a place of safety, but with the high incidence of infectious illness among their inmates this poses additional problems.

When there has been a disclosure by a child and there are other corroborative findings of sexual abuse, urgent action may be necessary to protect the child. On the other hand, where suggestive physical signs are found without corroborative evidence a more detailed evaluation is required. Some physical signs of sexual abuse have only recently been recognised. Although individual clinicians may themselves be highly suspicious (if not certain) that abuse has taken place, it does take time for these signs to gain credence among the generality of the medical profession. It has never been good medical practice to rely on just one physical sign. The recent guide prepared by the Standing Medical Advisory Committee provides the most authoratative assessment of the physical features of sexual abuse.[2] The amount of evidence that is required for clinical action involves a judgment about the balance of probabilities whereas the evidence that is required for legal action involves the findings being tested beyond reasonable doubt. What may be obvious to the clinician may still fail to meet this legal test. This fact must be borne in mind when planning the appropriate management of the child. Too often in the past social services departments have been accused of failing to act because of lack of evidence that would have enabled them to take the necessary legal action to ensure the safety of a child. Where such legal action has failed the child will remain in a damaging environment. Wynne and Hobbs have done much to draw attention to the physical signs of sexual abuse and continuing work and research is required for their evaluation.[3]

The problem posed by sexual abuse in Cleveland was precipitated into a crisis by the admission of a large number of children with their parents into a children's ward. The separation of the child from the family into a safe environment may secure corroborative evidence of sexual abuse by a disclosure from the child. Such a disclosure may take a considerable amount of time as the child needs to feel 'safe' to tell of his or her previous experiences. The application of a care order that relied on medical evidence alone, which could not measure up to the legal test, was bound to cause conflict. The increasing recognition of sexual abuse in Cleveland understandably resulted in the doctors and the professionals seeking more resources but there was no re-evaluation of whether the existing health care resources were being used appropriately as the report by the Lord Justice Butler-Sloss makes clear.

Interagency working through the committee structure recommended by the Department of

Health and Social Security (DHSS) document, *Working Together*,[4] was probably more advanced in Cleveland than other health districts in this country, but it is clear that faith in these procedures to solve the problems would be entirely misplaced. The DHSS has reacted with undue haste by issuing their guidelines set out in their document, *Working Together*, before the recommendations of the Butler-Sloss inquiry have been studied and thought through by all the professions involved. Having delayed issuing their document for some two years, such precipitate action parallels and will accentuate the mistakes made by all the professionals in Cleveland that we are all anxious to prevent.

As different agencies have their own particular responsibilities for children it is inevitable that problems of child sexual abuse have to be resolved through interagency cooperation. The report of Lord Justice Butler-Sloss and its detailed recommendations do need to be studied further. While the recommendation to establish specialist assessment teams is welcome, further consideration must be given to the teams' responsibilities. All the available doctors in each health district who have had any experience in the management of sexual abuse will be needed to be trained and helped but whether and by whom they should become 'approved' needs to be a matter for further discussion. Consultant paediatricians in community child health who are trained in social and educational aspects of paediatrics should have a leading role and be involved in the follow up of the children and their families. It is essential that this work forms part rather than the whole of their duties. There will be severe drawbacks to the formal process of 'approval' if it is adapted from the regulations under the Mental Health Act. It has also been proposed that cases involving allegations of sexual abuse made to the police about a child or third party relating to an offence that has taken place outside the 'family' should take place without the involvement of other agencies. Though in some cases this may be acceptable, as a general rule this recommendation is fraught with difficulties.

Lord Justice Butler-Sloss and her wise assessors are to be congratulated in providing a very careful, well thought out, and balanced report where any blame is identified equally among the various individuals and agencies concerned. By taking the middle ground, Lord Justice Butler-Sloss opens herself to attack from either extreme. There can be no doubt, however, that all those involved in the crisis in Cleveland acted with the best of motives. It is the strength of this conviction to work for the best interests of the child that now has to be applied to all the agencies working with the problem in each health district to try and construct both professional and interprofessional peer review buffers so that extremes of attitude or extremes of action are prevented. There is a delicate balance to be kept in applying measures designed to protect the children, which if applied wrongly may themselves cause such devastation to the children and their families. Interagency cooperation depends more on professionalism and personality than procedures. Building up teams of senior experienced professionals in each health district who can work together, fulfil their responsibilities, and know their limitations is the only way to try to get this balance right.

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Cytogenetic investigations of solid tumours of children

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SUMMARY The association of non-random chromosome abnormalities with solid tumours of childhood may improve accuracy of diagnosis and prognosis and lead to a better understanding of their biology. In a pilot study in the Northern region of England fresh tumour biopsy specimens were obtained from 39 of 72 consecutive solid tumours in children who presented over a period of 21 months. Cytogenetic analysis was possible in 33 and clonal chromosomal abnormalities were detected in nine. In addition, seven of 10 tumours investigated after treatment were abnormal. Ten of these 16 abnormal karyotypes have not previously been described. This pilot study has shown that a concerted investigation of tumour cytogenetics is possible. A multicentre study is essential if our knowledge of basic tumour cytogenetics is to progress.

Despite our ability to achieve prolonged remissions in most children with cancer, malignant disease remains second only to birth defects as the most common non-accidental cause of death in children over the age of 1 year in the United Kingdom. Accurate diagnosis is essential in order that appropriate treatment is used, but even within any one tumour category there remain variations in behaviour and response to treatment.

In the leukaemias some clonal cytogenetic abnormalities have already proved to be of diagnostic and prognostic value. For example, the translocations t(9;22), t(8;21), t(15;17), and t(8;14) help towards the diagnosis of chronic myeloid, acute myeloblastic, acute promyelocytic, and Burkitt's leukaemia respectively,[1] and clonal structural abnormalities are associated with a poor outcome in acute lymphoblastic leukaemia of childhood.[2] Studies of the oncogene c-abl in chronic myeloid leukaemia[3] and the relationship between c-myc and immunoglobulin gene loci in Burkitt's lymphoma[4] have led to a rapid increase in our knowledge of the molecular biology of haemopoietic malignancy.

Although clonal cytogenetic abnormalities have been reported in some solid tumours of children, much of the published information has appeared as single case reports. Cytogenetic investigations of solid tumours lag far behind those of leukaemias due to a combination of reasons including technical problems and the relative difficulty in obtaining viable tumour cells. One of the early steps in understanding the biology of malignancy, however, is to obtain a detailed knowledge of non-random chromosomal abnormalities of tumour cells. If the analogy with leukaemia is appropriate, then cytogenetic studies of solid tumours could provide diagnostic and prognostic information and the basis for a detailed study of the molecular events associated with their genesis.

In order that this baseline knowledge can be obtained a vigorous and comprehensive effort to study the chromosomes of all childhood solid tumours is required. We have embarked on a pilot study to obtain fresh material from most childhood solid tumours in the Northern region and carry out cytogenetic studies on these specimens. This report describes our initial results.

Methods

COLLECTION OF FRESH TUMOUR TISSUE

This was carried out in two phases. In January 1986 paediatric surgeons and pathologists within Newcastle were asked to inform us whenever a suspected tumour in a child was to be biopsied. We requested that the biopsy specimen be as generous as the surgeon could provide and be transferred fresh or in tissue culture medium (such as RPMI or Dulbecco's minimum essential medium) to a specified pathologist. A portion of the macroscopically viable tissue was transferred to the cytogenetics unit.

The second phase commenced in September 1986 when all paediatricians within the Northern region and many of the pathologists were invited by letter to participate.

The success in obtaining fresh tumour material was assessed by comparing the number of samples received with the total number of tumours notified to the Northern region Children's Malignant Disease Registry.[5]

CYTOGENETIC METHODS

Tumour was dispersed by gentle pipetting to provide a cell suspension for direct and short term cultures (one to 48 hours). Long term explant cultures were established in plastic Falcon flasks using various culture media (Ham's F-10, Chang's, and Leibovitz L-15, all supplemented with 20% fetal bovine serum) and incubated at 37°C. Colcemid exposure before harvesting varied between 0·2 µg/ml for 15 minutes for direct cultures and 0·01 µg/ml for four hours for long term cultures. Slide preparations were made by standard techniques and G banded with trypsin and Leishman's stain.

Results

COLLECTION OF FRESH TUMOUR TISSUE

From January 1986 to September 1987 inclusive, 72 new solid tumours occurring in children under the age of 15 years were notified to the Northern region Children's Malignant Disease Registry. Fresh tissue, either primary or metastatic, was obtained from 39 of these 72 solid tumours (table 1). During the same period fresh tumour was obtained from eight of 10 relapsed tumours from which tissue was available and from two of four children who had a biopsy of the tumour remaining after initial chemotherapy.

CYTOGENETIC ANALYSIS

Thirty seven specimens obtained at diagnosis were assessed; analysable metaphases were obtained from 33. One patient with a neuroblastoma had a constitutional abnormality [46,XX t(8;11) (q22.1;q21)]. Clonal cytogenetic abnormalities were found in nine comprising two neuroblastomas, two brain tumours, and one each of retinoblastoma, Ewing's sarcoma, Wilms' tumour, osteogenic sarcoma, and lymphoma (table 2). The remaining 23 were karyotypically normal apart from several single cell abnormalities.

Table 1 *Details of solid tumours presenting in the Northern region, January 1986–September 1987*

	No of children	*No in which fresh tumour tissue obtained*
Biopsy of primary tumour	50	24
Biopsy of metastatic disease	14	14
Biopsy of primary and metastatic tumour	1	1
No biopsy	7	—
Total	72	39

Analysable metaphases were obtained from six of eight relapsed tumours studied, five of which were abnormal and both specimens obtained from second look procedures had abnormal karyotypes. Overall 16 out of 47 tumours studied had abnormal karyotypes (table 2).

Discussion

The aim of this pilot study was twofold. Firstly it was to assess the feasibility of collecting fresh viable tissue from most childhood solid tumours in the Northern region and secondly, to carry out cytogenetic analysis of the specimens. This study has shown that both aspects are feasible with the cooperation of regional paediatricians, surgeons, and pathologists. Fresh material has been obtained from most tumours, and the use of a limited number of standard techniques by a single cytogenetics department has resulted in good quality analysable metaphase preparations in most cases.

No single culture technique has so far proved superior. Further experiments may show optimal culture techniques for each tumour type. Many of the cultures showed karyotypically normal cells. These may well represent non-malignant cells, such as fibroblasts, within the tumour. We believe, however, the clonal abnormalities obtained from tumour tissue at diagnosis did originate from tumour cells. Until larger numbers have been studied we cannot be certain that some clones do not represent a secondary abnormality, occurring in a genetically unstable tumour cell, brought about and selected by the culture conditions. Particular caution is necessary in interpreting clonal abnormalities in tissues that have been subjected to chemotherapy or radiotherapy, or both.

None the less, the cytogenetic abnormalities found in cells from a heavily pretreated neuroblastoma primary tumour,[6] bone marrow metastases from another, and spinal fluid seedlings from a relapsed medulloblastoma are characteristic of those in untreated tumours.[7] Also two of the clones (B and C) from a relapsed ependymoma (data not in table) resemble the abnormalities described in the only other published G banded case of this disease.[8] In all other cases, apart from the two remaining disseminated neuroblastomas, the abnormalities we have found have not previously been described. Of

Table 2 *Abnormal karyotypes from childhood solid tumours*

	Patient status at time of study	*Karyotype*
Primary tumour	*Long term cultures*	
Retinoblastoma	ND	46,XX/46,XX t(6;11)(p21.3;p1?5/92,XXXX
Osteogenic sarcoma	ND	46,XY t(2;3)(p13;q24)
Ependymoma	ND	45,XY,-16,t(6;16)/46,XY (~50% cells endoreduplicated)
Wilms' tumour	ND	51,XX,+8,+12,+12,+13,+17, 51,XX,+8,+12,+12,+13,+17,t(1;16)(p3;p22)
Wilms' tumour	PC	46,XY/46,XY,t(19;21)/46,XY,t(10;10)
Neuroblastoma	PC	46,XY/46,XY,1p+/46,XY,1p+,t(4;10),17p+
Primitive neuroectodermal tumour	R	46,XY,t(3;10),inv(7)(q32;p22)/46,XY,+ markers including ?del (2)(q31), ?t(1;18)(q1?;q21), inv(5)(q22;q23), ?del(14)(q22)
Ependymoma	R	6 different clones each with multiple markers*
Rhabdomyosarcoma	R	82,XX,+2,2,2,2,4,5,5,6,6,7,8,10,12,13, 14,15,15,18,18,19,20,21,22,22,+X,+M_1, M_2,M_3,M_5,M_5,M_6,M_7
Metastatic tumour (site)	*Direct cultures*	
T cell lymphoma (pleural fluid)	ND	45,XY+ multiple markers/87,XY+ multiple markers
Ewing's sarcoma (bone marrow)	ND	46,XX/45,XX,−7,−10,−21,−22,+M_1 ?del 7,M_2,+M_3 46,XX,−7,−22,+M_1,+M_2
Neuroblastoma (bone marrow)	ND	46,XX/polyploids with double minutes
Neuroblastoma (bone marrow)	ND	46,XX/polyploids with double minutes
Medulloblastoma (bone marrow)	ND	50,XX,+5,+6,+8,+13,−11,−17,−22,+11q, +22q,+i(17q)/49,XX,+5,+6,+8,−11,−17, −22,+11q+,+11q+,+22p+,+i(17q)
Medulloblastoma (cerebrospinal fluid)	R	46,XY/double minutes
Neuroblastoma (bone marrow)	R	46,XX/double minutes

ND=newly diagnosed; R=relapse; PC=postchemotherapy.
*Details of these clones are available on request.

particular interest is the primitive neuroectodermal tumour (PNET), full details of which are being published elsewhere.[9] Potluri *et al* have suggested that PNETs may be subdivided by their cytogenetic features into peripheral neuroepitheliomas with a t(11;22) and other PNETs showing other karyotypic abnormalities.[10] The tumour described here falls into the latter group.

This series of karyotypes highlights the current state of knowledge of cytogenetic abnormalities of solid tumours of childhood, each case constitutes a significant contribution to our knowledge. Although karyotypic abnormalities are being reported increasingly at international scientific meetings, most are published only as abstracts. Some patterns have begun to emerge. In retinoblastoma, isochromosome 6p appears to be a unique abnormality,[11] and the one case of retinoblastoma in the present series also had an abnormality of chromosome 6. Alveolar rhabdomyosarcomas are associated with t(2;13),[12] and evidence suggests that 3p 14 –> 21 may be a non-random site for change in this disease.[13] In addition to PNETs t(11;22) is associated with Ewing's sarcoma in some but not all cases.[14] This association raises the possibility that Ewing's sarcoma and some forms of PNETs have a common origin. In translocations involving chromosome 22 the breakpoint arises in the region of the oncogene c-cis.[15] The Ewing's tumour described in this report did not have this translocation but did have an abnormal chromosome 22.

The association of aniridia and Wilms' tumour has been linked with constitutional deletion of 11p13. Abnormalities of this chromosomal region have been detected in some Wilms' tumours from children with a normal constitutional karyotype.[16] Additional abnormalities of chromosomes 1 and 16 may occur in advanced tumours.[16 17] Recently the combination of hyperdiploidy, complex chromosomal translocations, and an anaplastic histological appearance of Wilms' tumour have been associated with a particularly poor prognosis.[18]

After leukaemias, brain tumours remain the single largest group of malignancies in children. Until recently investigation of these tumours has been hampered by problems of nomenclature and classification. Others have already begun to approach the problem of improving diagnosis and prognosis and understanding their biology by undertaking cytogenetic investigations.[19]

The differential diagnosis of small round cell tumours of childhood includes rhabdomyosarcoma, lymphoma, Ewing's sarcoma, and neuroectodermal tumours. Despite the increasing use of specialised investigations, including monoclonal antibodies and electron microscopy, the identity of some tumours remains obscure.[20] As in haemopoietic malignancy, cytogenetic investigation of solid tumours may emerge as an important diagnostic tool. At present prognostic factors in most children with solid tumours are limited to clinical and histopathological staging and in some cases histological subtyping.[21 22] Cytogenetic abnormalities may provide additional prognostic information, but until many hundreds of tumours have been karyotyped we cannot begin to approach the level of diagnostic and prognostic value that now exists for leukaemias. Despite this relative lack of knowledge, the ability to detect cytogenetic abnormalities in metastatic sites and treated primary tumours may improve the accuracy of staging procedures and assessment of response to treatment.[6] This comparatively simple aspect of the value of cytogenetic investigations has so far not been exploited.

In conclusion, it is recommended that biopsy material from tumours in children should never automatically be put into formalin. The Northern region pilot study has shown that fresh biopsy material can be obtained from most childhood solid tumours and cytogenetic investigation can be successful in a wide variety of cancers. Cooperation between groups of workers in the field of paediatric oncology could lead to multicentre studies of fundamental aspects of the biology of childhood cancer, one of which is the investigation of cytogenetic abnormalities.

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Clinical presentations of Ehlers Danlos syndrome type IV

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SUMMARY Ehlers Danlos syndrome type IV is an often lethal disease caused by various mutations of type III collagen genes. It presents in infancy and childhood in several ways, and the symptoms and signs include low birth weight, prematurity, congenital dislocation of the hips, easy inappropriate bruising (sometimes suspected as child battering), and a diagnostic facial phenotype. These features predict a lethal adult disease often complicated by fatal arterial rupture in early or middle adult life. Most affected patients can be diagnosed from radiolabelled collagen protein profiles by polyacrylamide gel electrophoresis. Prenatal diagnosis by specific type III collagen restriction fragment length polymorphisms is possible in some families, and will become increasingly important. Prenatal diagnosis and prevention of the disease in selected families is already possible and will be widely available in the future.

Ehlers Danlos syndrome is an heterogeneous disorder of connective tissue characterised by abnormalities in the skin, ligaments, the pleuroperitoneal linings of the gastrointestinal tract, and the cardiovascular system. Of more than nine different forms of the disease type IV is particularly dangerous, often being complicated by lethal rupture of small and medium sized arteries later in life.[1] First described by Barabas[2] as the arterial type, and Beighton[3] as the ecchymotic variant of Ehlers Danlos syndrome, specific molecular abnormalities were first identified in 1975.[4] The clinical range is wide and there are autosomal dominant and recessive forms of the disease. The so called 'acrogeric' form has a much worse prognosis than the ecchymotic form which probably has some degree of overlap with the Ehlers Danlos syndrome type I syndrome.[1] With the advent of recombinant deoxyribonucleic acid (DNA) technology, and advances in molecular biology, the gene for human type III collagen has been cloned firstly as a cDNA covering the 3′ end,[5] and more recently as full genomic sequences.[6] At least two restriction fragment length polymorphisms have been identified with which the mutant locus can be traced in suitable families. The way is therefore open for prenatal diagnosis and prevention of this disease, and because it often presents in childhood in a diverse and sometimes remarkable fashion we describe here the essential physical attributes as seen in infancy, childhood, and adolescence by paediatricians, rheumatologists, dermatologists, geneticists, and general practitioners. Sometimes these patients present first as new mutations, and at other times as members of affected families in which the disease has already been diagnosed in adults. Some patients presented to us in childhood, but in others the childhood history and clinical photographs of the adults were sufficiently interesting and relevant that we have included them.

Case reports

CASE 1

A boy was born prematurely at 35 weeks' gestation weighing less than 2000 g. He had a cerebral haemorrhage, and then developed hydrocephalus. At birth he had a tight amniotic band deforming his right lower leg. His mother subsequently died at the age of 30 after a massive retroperitoneal haemorrhage from a ruptured aorta. Photographs of the mother showed the typical features of acrogeric Ehlers Danlos syndrome type IV with large eyes and peaked nose, and premature aging of the hands (acrogeria).

Examination of radiolabelled collagens from the child's cultured skin fibroblasts showed the typical profile of acrogeric Ehlers Danlos syndrome type IV (fig 1). The mother was the tenth of 11 children and

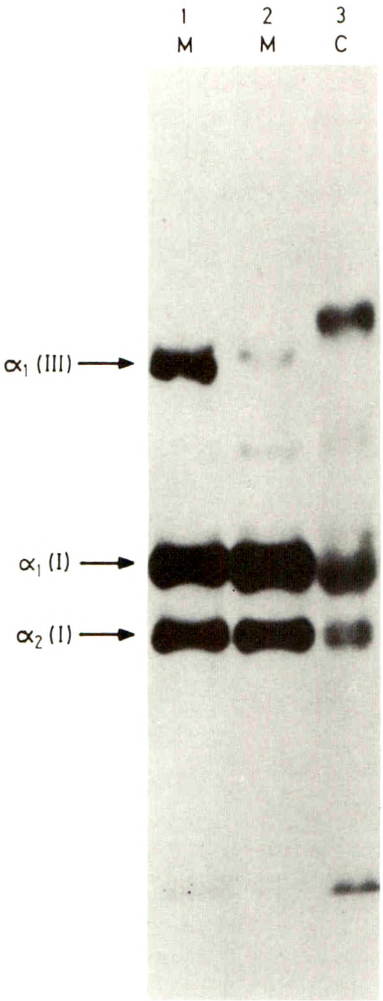


Fig 1 *Radiolabelled ^{14}C labelled collagen profile of case 1. Note intracellular retention and poor secretion of the mutant protein in tracks 2 and 3 compared with normal control in track 1.*

had normal parents and siblings. Her father was 43 years old when she was born, and presumably the gene defect transmitted to her son was a new autosomal dominant mutant.

CASE 2

A girl was delivered by caesarean section (because of abruptio placentae and fetal distress) at 38 weeks' gestation of her mother's first pregnancy; she weighed 2005 g. Her parents were second cousins. At birth she was noted to have unusual facies, dislocated right shoulder and hip and scanty subcutaneous fat. She subsequently failed to thrive, developed serious feeding difficulties, and was transferred to Great Ormond Street hospital. An electroencephalogram showed an abnormal focal disturbance, and subsequent epileptic fits were reasonably well controlled with phenobarbitone. Chromosomes showed a normal 46XY karyotype. Her feeding difficulties were partially caused by a hiatus hernia and a malrotated stomach.

She had extremely thin and soft atrophic skin with a prominent venous pattern (fig 2). Her joints dislocated easily, especially the hips and the shoulders, and her feet were long and looked somewhat delicate. She subsequently developed severe gastroenteritis and died. Necropsy was not done.

CASE 3

A baby boy was born prematurely at 30 weeks' gestation after premature rupture of the membranes. He was the youngest of four children with completely normal siblings and parents. He had bilateral dislocation of the hips that responded well to conservative splinting. He was also noted to have generally thin skin and long, delicate fingers and toes that were somewhat hyperextensible, a phenotype similar to case 2 (fig 3a). When next seen (at the age of 18 months) he was in hospital because of excessive, unexplained, persistent bruising. Examination showed the typically large eyes and pinched nose of acrogeric Ehlers Danlos syndrome type IV (fig 3b). Except for being slow to walk he was otherwise physically normal. Because of his parents' extreme anxiety he has not been followed up regularly but at the time of writing had developed no further complications.

CASE 4

A 3 year old boy was referred with suspected Ehlers Danlos syndrome type IV. His mother had joint laxity, anorexia nervosa, and a history of spontaneous rupture of the anterior tibial artery. The history was complicated by suspected battering of the child by his father and he had been admitted to the local paediatric department at the age of 2 months with a fractured shin, a large right parietal bruise, and a subdural haematoma. He also had fractures of the lower end of the left tibia and fibula, and excessive bruising of his neck and face. Subsequently he showed some developmental delay and at the age of 21 months had an estimated developmental age of 14 months and a speaking age of 9 months. Having weighed only 2500 g at birth, he remained close to the 50th percentile for weight.

When examined at the age of 3 he showed clear physical characteristics of Ehlers Danlos syndrome with a broad forehead and feet and obvious joint

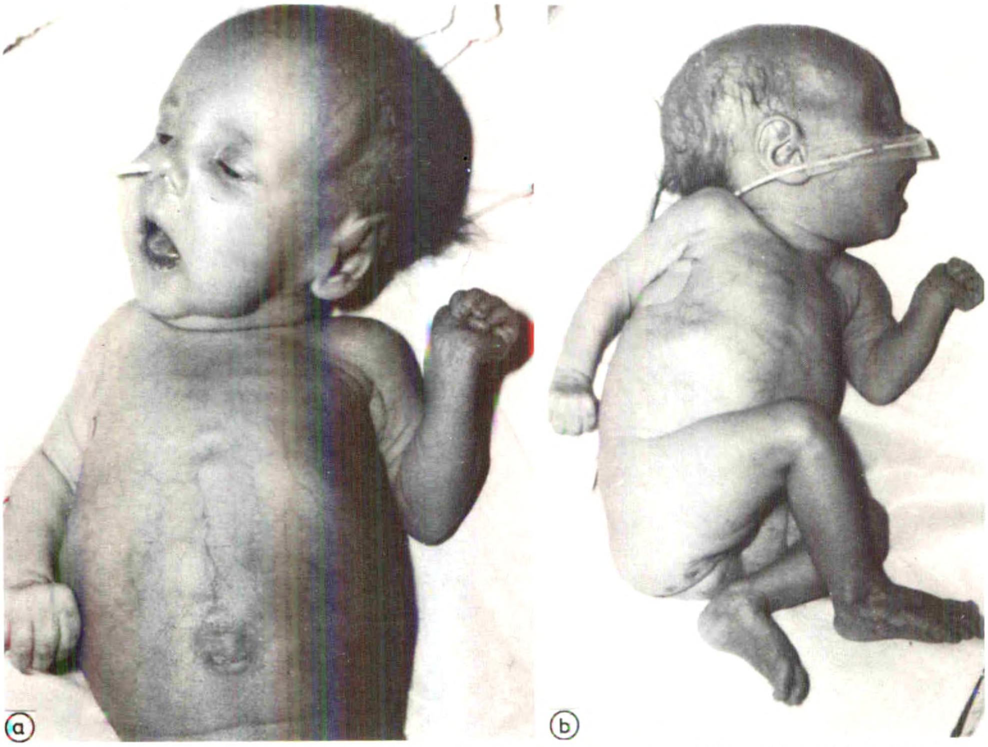


Fig 2 *Case 2: note generally thin wrinkled skin with prominent venous network, and long delicate feet.*

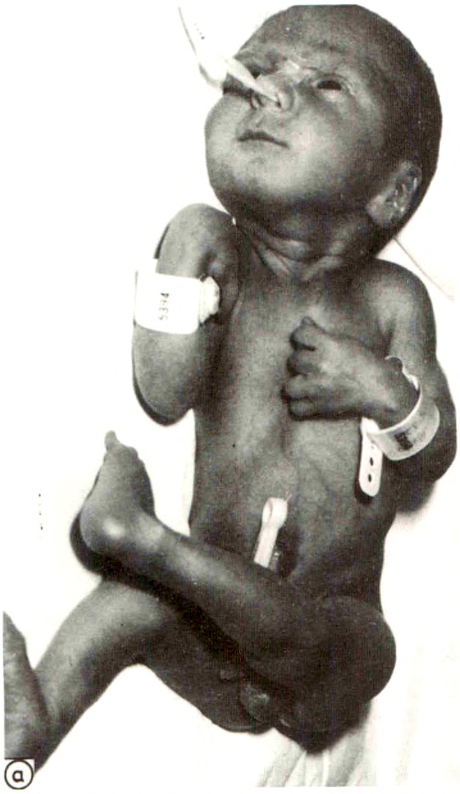
hypermobility (figs 4a and 5a and b). We did not consider his facial features diagnostic of acrogeric Ehlers Danlos syndrome (case 1) but provisionally classified him as type II or III Ehlers Danlos syndrome. Subsequent investigations clearly placed him in the Ehlers Danlos syndrome type IV group. Firstly, cultured skin fibroblasts showed typical failure to secrete type III collagen into the medium with retention of a slightly higher molecular weight molecule in the cell layer (fig 6). Clinical photographs of his mother's face and hands (figs 4b and 5c) showed unmistakable acrogeric (lethal) Ehlers Danlos syndrome type IV. Clearly this gene had been inherited as an autosomal dominant, but presented atypically in childhood.

CASE 5

A 7 year old girl was referred by a dermatologist to whom she had been sent for assessment of non-haematological bruising and a suspected history of non-accidental injury. She had bruises on the limbs and trunk and poorly healed scars on her legs. Her skin was transparent with clearly visible superficial capillary and venous systems. She also had a thin nose and lips, and large prominent eyes. Her 13 year old brother had similar features and was also clearly recognisable as being affected from a photograph taken at the age of 2. Both children had been small babies (less than 3000 g when born at full term). Their mother (fig 7) showed the typical clinical features of acrogeric Ehlers Danlos syndrome type IV, without serious complications except for flexion contractures of the interphalangeal joints of her hands, and severely clawed feet as a result of tendon contractures causing flexion deformities of the metatarsophalangeal joints. Her facial features in childhood (fig 7a) had been identical to theirs; there was no other relevant family history.

CASE 6

A 9 year old boy presented incidentally when we examined his mother who had typical acrogeric Ehlers Danlos syndrome type IV. He had weighed 2900 g when born at full term and up to the time of examination had had no problems. He had two normal elder siblings. He also was clearly recognisable as having Ehlers Danlos syndrome type IV. His mother subsequently had an operation for rectal prolapse, ruptured her iliac artery and vein, and died.



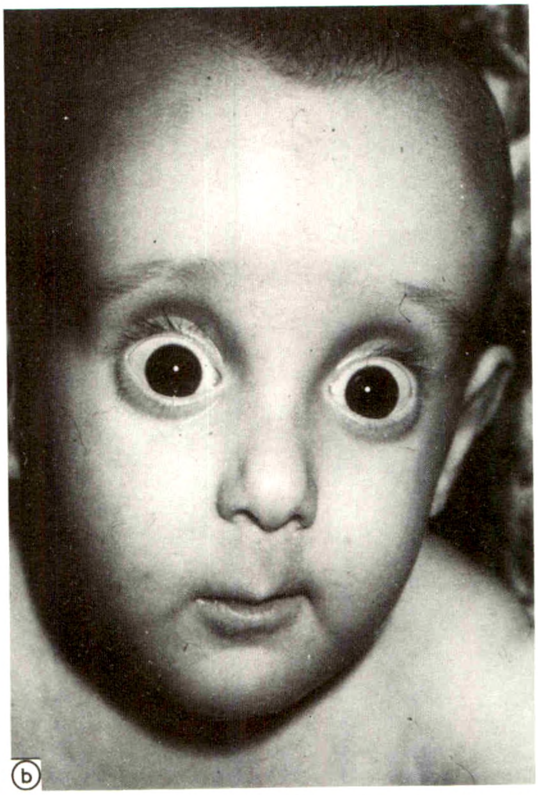


Fig 3a *Case 3 at 34 weeks old when appearance is not diagnostic showing only thin skin and somewhat long feet similar to fig 2.* Fig 3b *Case 3 aged 18 months with the characteristic facial appearance of acrogeric Ehlers Danlos syndrome type IV (large eyes, and thin nose and lips).*

CASE 7

An 8 year old girl presented in 1979 to the local hospital with a history of persistent bruising since childhood. Detailed haematological examination was normal and she showed features suggestive of the Ehlers Danlos syndrome. When examined by us she did not show the facial features of acrogeric Ehlers Danlos syndrome type IV but had large eyes and thin skin. Her father, who had a history of bilateral recurrent pneumothoraces, also had thin skin prominent varicose veins, hypermobility of the joints, and large eyes. Neither patient has had any further problem at the time of writing, even though their tissues contained only traces of type III collagen and produced little from cultured skin fibroblasts.

CASE 8

A Cretan girl presented as a teenager with a history of having bruised easily and been loose jointed from the age of 3. She had weighed 3400 g at birth, the pregnancy had been normal. Noticeable clinical features included large, prominent eyes with blue sclerae similar to those in cases 4 and 6. Unlike them she showed extensive haemosiderotic staining of the anterior shins (figs 8a, b, c, and d). She had rather prominent capillary telangiectasia, and prominent venules over her upper anterior chest. Her otherwise normal mother had loose jointed fingers and a lax lumbar spine. Radiolabelled collagens from both mother and daughter showed somewhat diminished type III collagens (fig 8e) secreted into the medium (these were about 60–70% of the expected control secretions). In contrast to the acrogeric pattern of Ehlers Danlos syndrome, there was no abnormality of collagen secretion.

CASE 9

An unusual 11 year old girl was referred by a geneticist with a history of persistently low weight and short stature. She had continued below the 3rd centile and skeletal dysplasia had been suspected (particularly the Leri-Weil syndrome). Another unusual feature was rather sparse scalp hair, but in

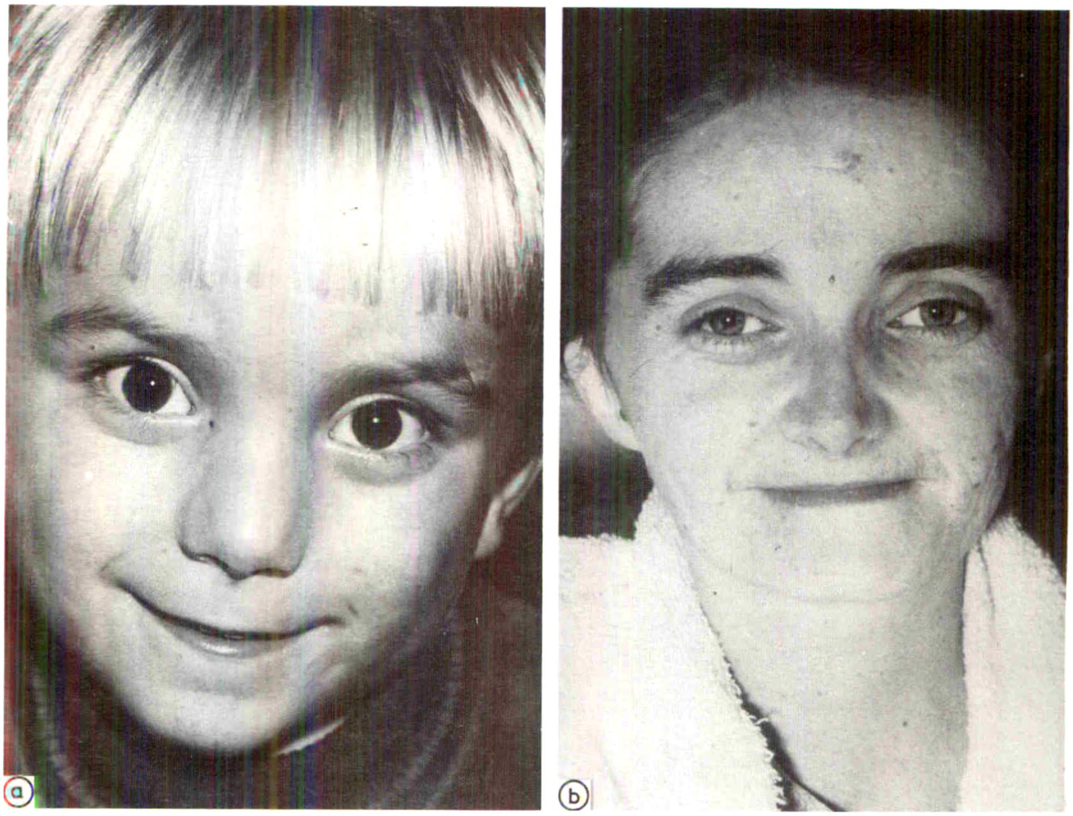


Fig 4a *Face of case 4 showing broad forehead more suggestive of Ehlers Danlos syndrome type I or II.* Fig 4b *Mother of case 4: facial phenotype is clearly that of acrogeric Ehlers Danlos syndrome type IV.*

other respects she had typical Ehlers Danlos syndrome type IV. Collagen analysis showed type III collagen deficiency without retention.

CASE 10

A 9 year old girl was born weighing 2800 g at 37 weeks' gestation. Her mother immediately suspected an abnormality and subsequently the child persistently bruised easily. Acrogeria was diagnosed by her local dermatologist. Examination at the age of 10 confirmed typical acrogeric Ehlers Danlos syndrome type IV. Her cultured fibroblasts made no type III collagen (as measured by carboxymethyl cellulose chromatographs of radiolabelled collagens). At the time of writing she was of childbearing age, and anxious to have accurate genetic counselling.

CASE 11

This 6 year old girl was the third generation of her family to be affected with acrogeric Ehlers Danlos syndrome type IV. Though many family members had died of the arterial complications of the disease, hers was biochemically atypical. Measurement of type III collagen showed a 10–20% reduction in the quantity of normally sized protein. Subsequently we studied the familial segregation of a collagen ava II restriction fragment length polymorphism using a 3′ human type III cDNA as probe. This accurately predicted the disease and will be used in future for prenatal diagnosis and prevention in this family.

The patient's abnormal physical signs included large eyes, a pinched nose, and a tendency to bruise abnormally. The phenotype of her adult family was similar. At the time of writing the child had developed no complications but undoubtedly she is at high risk of spontaneous arterial rupture in early middle age.

CASE 12

A 13 year old girl presented to the casualty department of her local hospital in The Netherlands with a migrainous headache. This resolved but shortly afterwards she had a transient left hemiplegia. An emergency arteriogram showed an 'in and out'

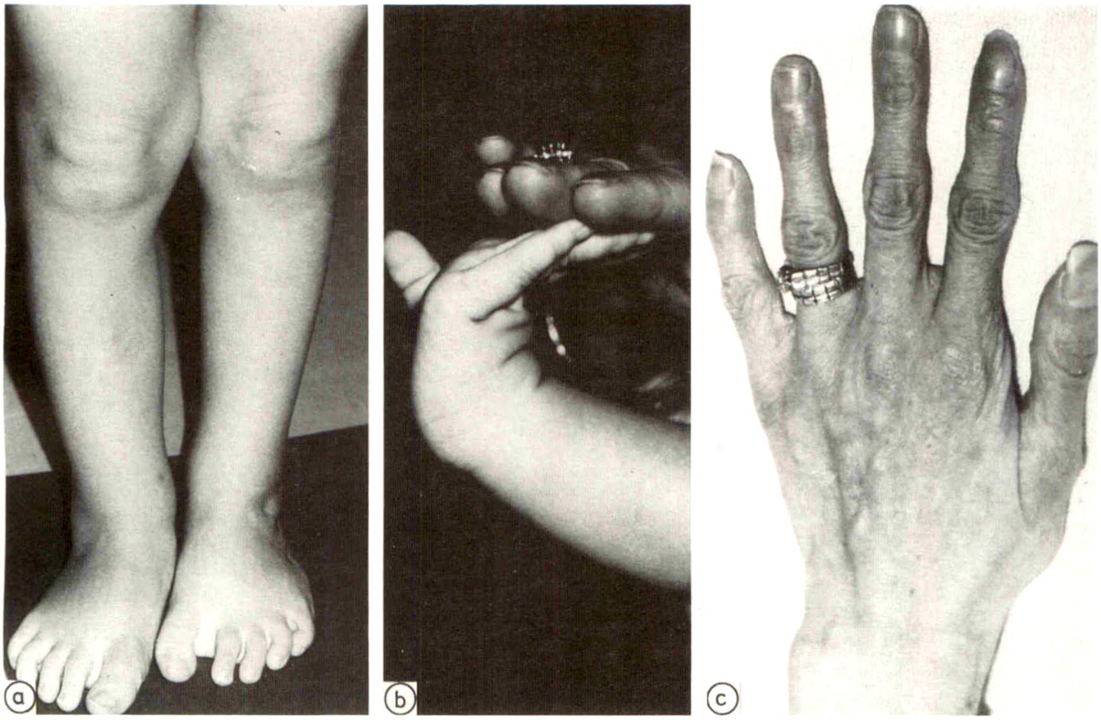


Fig 5a and b *Broad feet and loose jointed hands of case 4.* Fig 5c *Acrogeric hands of mother of case 4.*

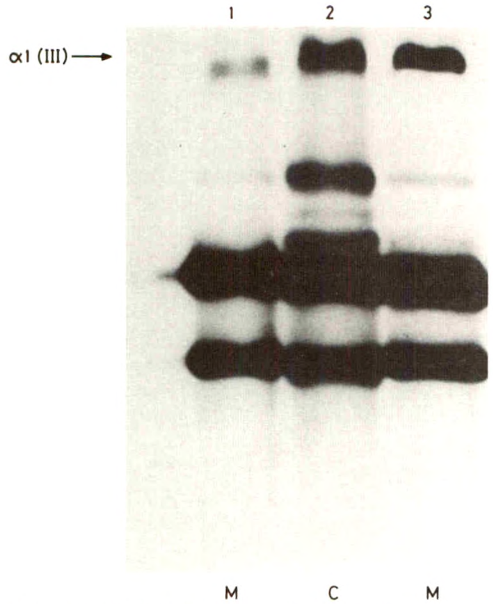


Fig 6 *Radiolabelled collagens from case 4 separated in 5% polyacrylamide slab gels. Note poor secretion and abnormal retention (tracks 1 and 2) compared with normal control (track 3), which is typical of acrogeric Ehlers Danlos syndrome type IV.*

dissection of the right internal carotid artery, and a computed tomogram showed partial necrosis of her right internal capsule. She made a complete recovery without residual signs. Physical examination showed the classical facies of acrogeric Ehlers Danlos syndrome type IV with large eyes, a pinched nose, and a madonna-like facies. Photographs taken when she was a baby clearly showed a recognisable phenotype. The biochemical investigations show a 50% reduction of type III collagen without intracellular retention, which clearly distinguishes her from the usual acrogeric pattern.

CASE 13

A 33 year old woman died of an undiagnosed rupture of the splenic artery having been treated conservatively for suspected cholecystitis. Previous events had included a ruptured liver after the birth of her only normal child, though no severe problems had arisen during the pregnancy. Examination of childhood photographs show the diagnosis to be quite obvious in babyhood and childhood as well as in adult life (figs 9a, b, and c). Silver-Russell dwarfism had been suspected as she had always been a small child (below the 3rd percentile for height and weight). Biochemical investigation showed no type III collagen contained in tissue or produced in

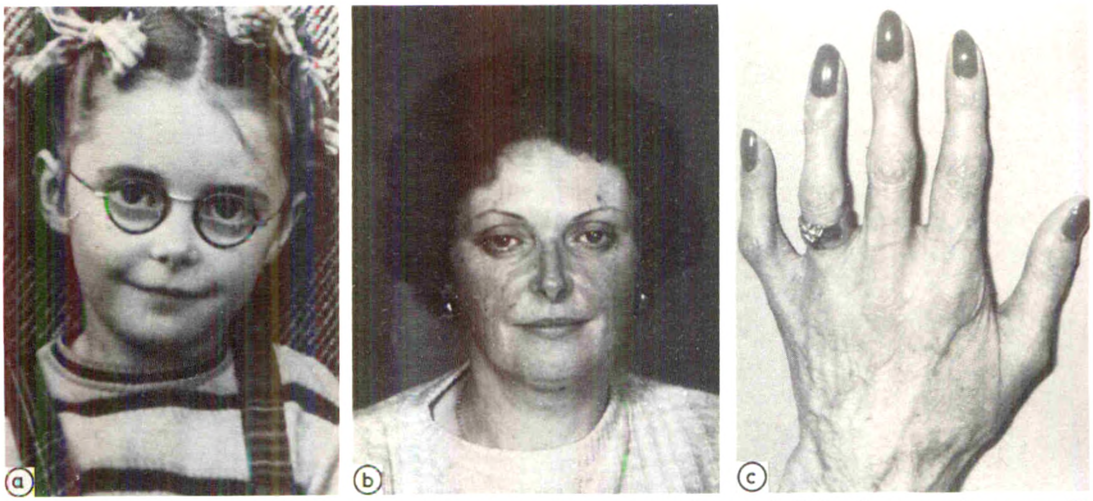


Fig 7a and b *Childhood and adult facies of mother of case 5 showing typical acrogeric Ehlers Danlos syndrome type IV: note large eyes and thin nose.* Fig 7c *Typical prematurely aged hand of case 5.*

culture. She had intracellular retention of the protein typical of acrogeric Ehlers Danlos syndrome type IV.

CASE 14

A girl aged 7 was described to the Section of Paediatrics of the Royal Society of Medicine as an example of acrogeria.[7] Her photographs at the time showed the typically thin skin and facies of acrogeric Ehler Danlos syndrome type IV (figs 10a and b). Her subsequent history has included recurrent bilateral pneumothoraces (treated by pleural stripping), a spontaneously ruptured spleen, and a ruptured left renal artery that was treated by nephrectomy. She also had a miscarriage at 16 weeks' gestation of her only pregnancy. Other complications included severe shortening of the right achilles tendon causing severe talipes equinovarus. At the time of writing she was 37 years old and had had no other serious complications. Her biochemical investigations showed a typical failure to secrete type III collagen that is retained in abnormal quantities intracellularly.

CASE 15

A young man died at the age of 16 of a ruptured aorta with dissection upwards into the subclavian artery and downwards in the abdominal aorta below the renal artery. He had the classical features of acrogeric Ehlers Danlos syndrome type IV with the typical facies and profile of the disease (figs 11a and b). Detailed investigation of the family showed the autosomal recessive segregation of type III collagen deficiency. He was the first patient in whom molecular abnormalities of type III collagen were described.[4, 8]

Discussion

Ehlers Danlos syndrome type IV (also called acrogeria, and the ecchymotic arterial form of Ehlers Danlos syndrome) is clearly one of the inherited connective tissue diseases with unique clinical characteristics and a specific biochemical profile of abnormalities of type III collagen.[8, 9] The disease is usually easily recognisable and can present with low birth weight, and subsequent failure to thrive with small stature and low weight. Joint dislocations, and severe bruising with thin skin and capillary prominence or telangiectasia, are common. The facies and general characteristics of the severe acrogeric pattern are unmistakable (cases 1, 2, 5, 9, 11, 12, 13, 14, 15, 16, and 17). Rather surprisingly case 3 was not diagnosed as acrogeric in childhood, though his mother was clearly in this group. The milder cases (4, 6, 7, 8, and 10) were in general easily recognised.

Modern molecular biology has made possible the complete understanding of the molecular basis of this group of diseases, and we already know that the acrogeric group (with intracellular retention and no secretion of type III collagen) are different from the ecchymotic group (who usually produce diminished amounts of normally secreted protein that is not retained intracellularly). Case 13 is exceptional in having an ecchymotic biochemical profile but the

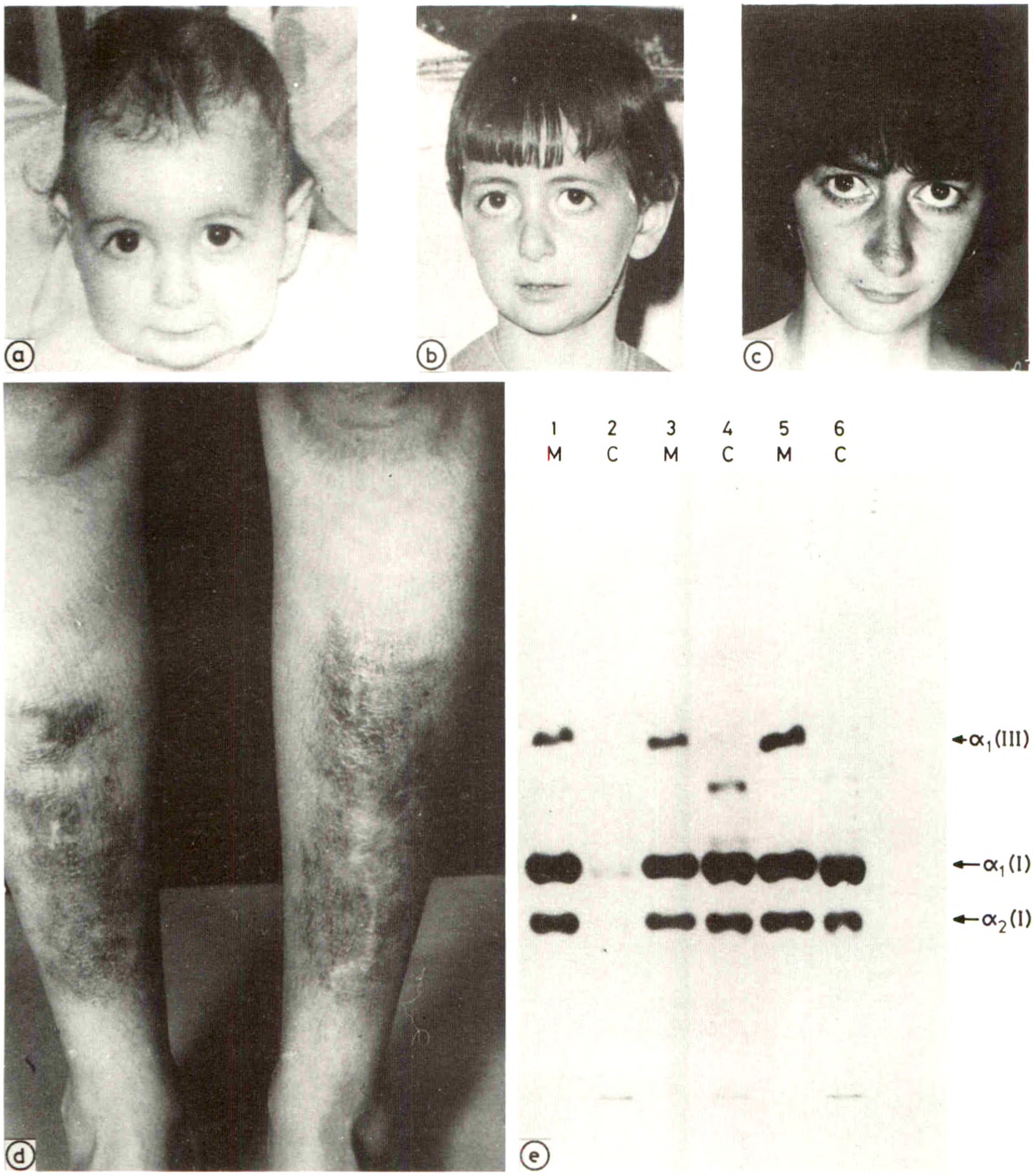


Fig 8a, b, and c *Baby, childhood and adolescent facies of case 8.* Fig 8d *Pretibial ecchymoses in adolescence (case 8).* Fig 8e *Biochemical changes (case 8) show only lowered medium collagens tracks 1 and 3 compared with control in track 5. Neither patient nor control (tracks 2, 4, and 6) retain radiolabelled material intracellularly.*

acrogeric (vascular rupture) phenotype. Probably all patients deficient in type III collagen are at risk of vascular rupture, but this is invariable and often fatal in the acrogeric group.

The gene for human type III collagen has been cloned both as cDNAs for the 3′ and 5′ ends and as long genomic fragments.[5 6] At the time of writing two protein mutations had been identified in patients with Ehlers Danlos type IV. The first produces a site abnormally susceptible to pepsin in what seems to be a lengthened protein[10]; the second produces a large deletion that results in a mutant protein of 5/7

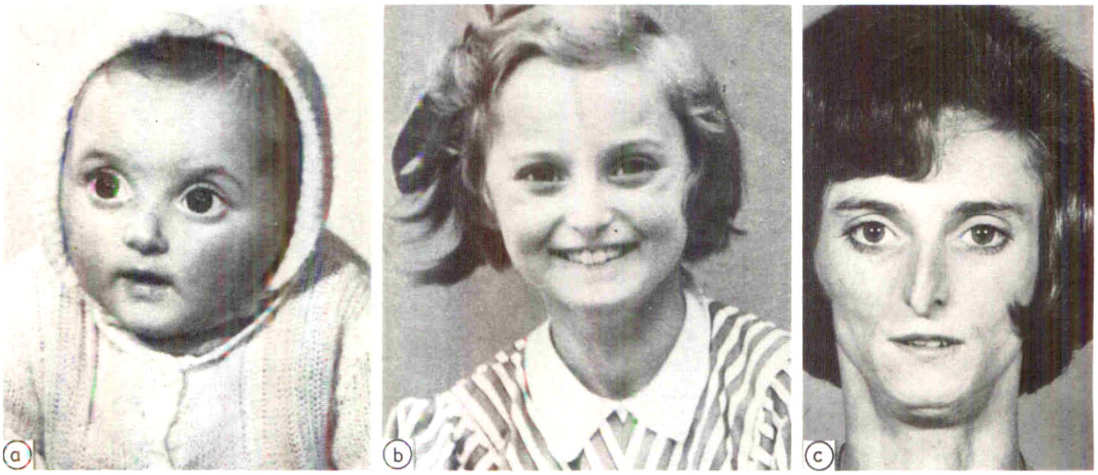


Fig 9a, b, and c *Baby, childhood, and adult facies of case 13 showing typical acrogeric Ehlers Danlos syndrome type IV. The diagnosis is unmistakable in all three pictures.*

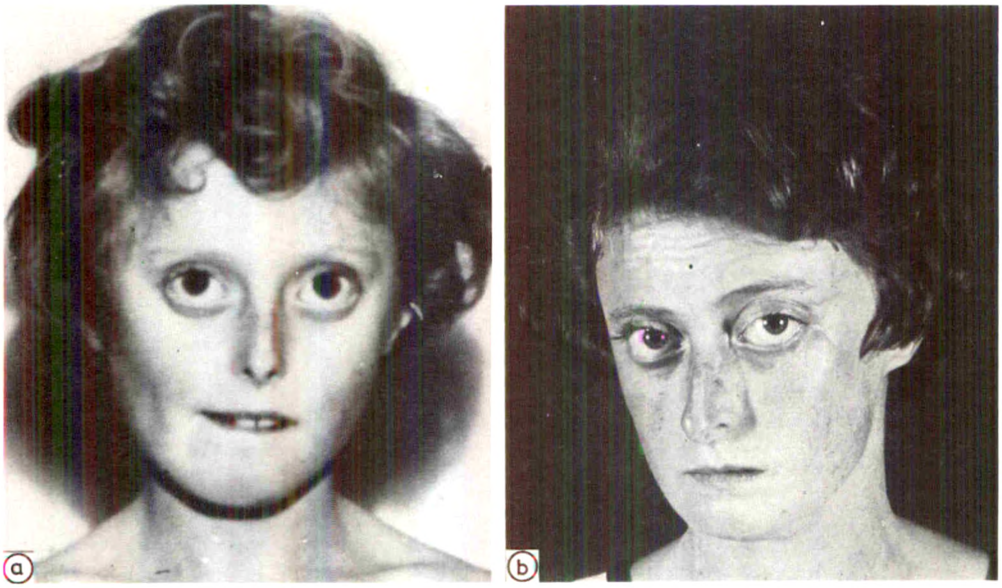


Fig 10 *Childhood and adult facies of case 14. Both show unmistakable acrogeric Ehlers Danlos syndrome type IV. The childhood photograph was originally published in 1957.*[11]

the normal size, and a large deletion in mRNA and genomic DNA seen on Northern and Southern blotting.[11] So far we have found only quantitative abnormalities in type III collagen mRNA (in case 13) and no evidence of major deletions. Probably the mutations causing the obvious protein abnormalities are subtle and therefore difficult to detect, but recent rapid advances in molecular biological techniques suggests a strong likelihood that we shall be able to identify them in the reasonably near future. There appear to be a number of clinical and genetic subgroups of this disease and at least five separate types are likely. The clinical features of so called acrogeria as described by Gottron[12] and Bazex and Dupre[13] are identical to those described as acrogeric Ehlers Danlos syndrome type IV. Bazex

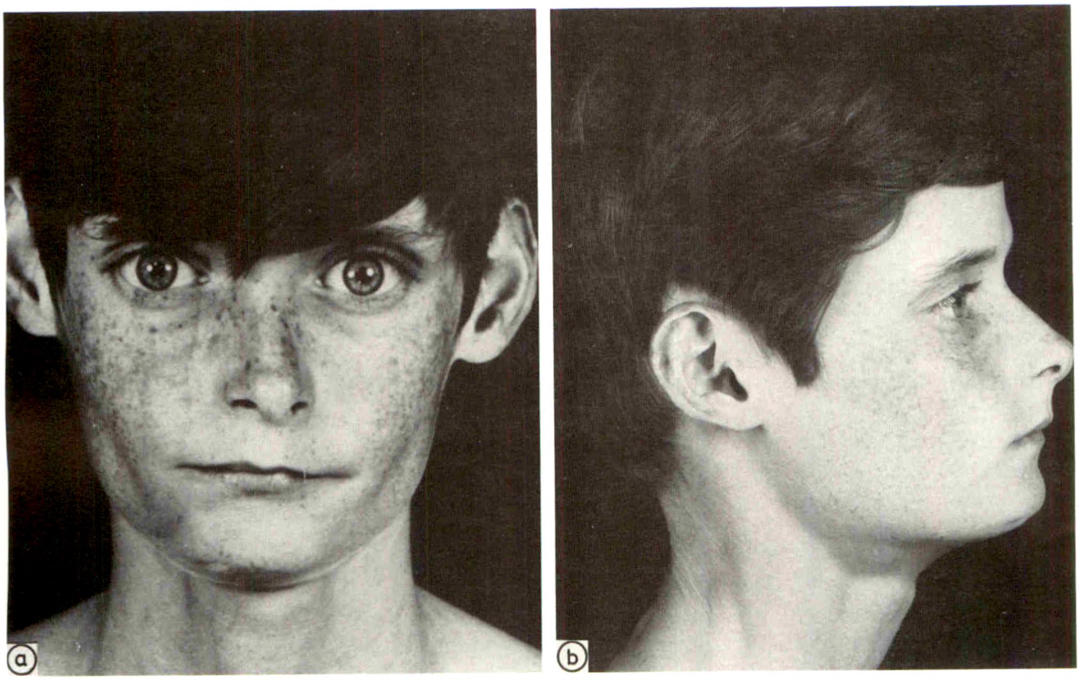


Fig 11 *Front face and profile of first patient with acrogeric Ehlers Danlos syndrome type IV in whom type III collagen deficiency was discovered.*

and Dupre's original patient was identical to those patients with acrogeric Ehlers Danlos syndrome type IV (figs 6, 7, 9, 10, and 11).

The differential diagnosis includes other forms of Ehlers Danlos syndrome, especially types I, II, III, and VII. Type VII may be completely separated on clinical grounds and the persistence of procollagen extension sequences produced in culture or contained in tissues that are resistant to pepsin. The specific finding of type III collagen mutations exclude the other types, so that type III collagen mutations stand apart both clinically and biochemically.

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A profile of abuse

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SUMMARY Of 260 children considered to have been the victims of child abuse or neglect, or both, 149 suffered non-accidental injury, 71 had evidence of growth problems, 87 had developmental and speech delay, and 63 showed evidence of appreciable behaviour disturbance. While the overall prevalence of development and behaviour problems in the series was high there were particular associations noted between growth problems and developmental delay, between increasing age and behaviour disturbance, and between evidence of emotional deprivation and both behaviour disturbance and developmental delay. Children with non-accidental injury but without growth problems or emotional deprivation were least likely to show behaviour or developmental problems.

The features associated with child abuse and neglect can be classified according to whether they describe factors that cause the abuse (primary) or its consequences. Thus primary factors (causative) such as parental violence, sexual deviance, or lack of attention lead to understimulation and emotional deprivation; poor feeding practices or poor physical care may lead to identifiable injuries, sexual abuse, behaviour disturbances, intellectual impairment, failure to thrive, and evidence of physical neglect, respectively. It is important to distinguish between these two categories as the first only indicates that circumstances exist, which might have consequences for the child, while the latter provides evidence that the child has actually suffered harm. It is common knowledge that some children seem to escape the consequences of living in depriving and abusing families relatively unscathed. A child given loving care and attention by one partner but who is persistently sexually abused by another is likely to suffer as severe behaviour problems as a child subjected to severe emotional deprivation. Isolated episodes of neglect or even violence may be much less damaging to long term development than persisting chronic mismanagement.

There is little information about the interrelation of various forms of abuse and neglect. The present report is a descriptive analysis of 260 children who have been the subjects of child abuse presenting to the Children's Hospital in Sheffield over a period of 10 years.

Patients and methods

The sample consisted of all children with clinical evidence of abuse and neglect referred to one paediatrician (LST) between 1975 and 1986. The children were seen either in outpatient clinics or after admission to the ward. All the children had suffered either non-accidental injury, sexual abuse, non-organic growth problems in association with adverse home circumstances, developmental or speech delay not due to any intrinsic defect, gross physical neglect, or various combinations of these at either the time of initial assessment or subsequent follow up. No child was included in the series unless at least one of these findings was present. Additional findings included in the study are behavioural and emotional problems and evidence of emotional deprivation.

DEFINITION OF PROBLEMS

Growth

The children in this category were included on the basis of our definition that has been reported in a previous study.[1]

Developmental/speech delay

Three categories of cases came under this heading:

(1) Children under 2 years of age (57% of the series) who underwent standard developmental screening either by the Denver method[2] or that of Illingworth.[3] Children who were at least four months behind chronological age in social and cognitive development including speech were classed as having developmental delay. All these children had normal psychomotor milestones.

(2) Children over 2 and under 5 years of age (28%) with delayed speech who were assessed by a speech therapist who considered that active intervention was required.
(3) Schoolchildren (16%) whose learning skills were considered sufficiently impaired to require special help.

All the preschool children with developmental delay had impaired speech development—that is, impairment in language development but not including problems of articulation. In all these cases alternative explanations for developmental and language delay were considered and 15 children with problems such as hearing loss, global delay beginning in early infancy, and syndromes associated with mental retardation were excluded from this part of the analysis.

Emotional deprivation
In addition to clinical evidence of possible abuse and neglect on examination evidence of one primary (causative) factor, emotional deprivation, was considered. Evidence for this depended on descriptions by community doctors, health visitors, general practitioners. and social workers in either reports or minutes of previous case conferences concerned with the child and its family. These observations included statements that parents did not hold, cuddle, speak to, or play with the child and that they did not respond in an appropriate way to their needs or showed excessively rigid attitudes to such matters as behaviour or cleanliness.

Behavioural or emotional problems
These children fell into three categories:

(1) Those who were referred independently of the authors to child psychiatrists or psychologists and assessed as being sufficiently disturbed to require further help.
(2) Children who on admission to hospital were noted to be disturbed and whose problems were confirmed by a child psychiatrist.
(3) Children whose behaviour at school led to some sort of action such as exclusion from class, transfer to a special school for emotionally disturbed children, or to residential care.

As this was not a prospective study and concerned follow up of children over many years, no formal assessment of behaviour was carried out but all cases in this category were considered by independent agencies or services to be appreciably disturbed.

Statistical analysis was by χ^2 with 95% confidence intervals based on the odds ratio, and Mann-Whitney U test.

Results

There were 260 children in the series referred to the Children's Hospital, Sheffield between 1975–86. Table 1 summarises the various categories of abuse in the series, the percentage of children in each category initially, their mode of referral, and the prevalence of various forms of abuse and neglect after investigation.

One hundred and fourteen cases out of 129 that were initially diagnosed as non-accidental injury were referred by emergency services (88%) whereas cases of growth problems were referred mainly by primary care services, general practitioners, and health visitors (34 out of 47 cases; 72%).

After the initial diagnosis more cases were recognised either at first assessment or during subsequent follow up: non-accidental injury, 20 (13%), growth problems, 24 (34%); emotional deprivation, 69

Table 1 *No (%) children with primary diagnosis at first examination in relation to nature of referral and prevalence of features of abuse after full assessment (n=260)*

Nature of referral	*All cases*	*Non-accidental injury*	*Growth problems*	*Emotional deprivation*	*Physical neglect*	*Emotional and behavioural problems*	*Speech/ developmental delay*	*Sexual abuse*
Emergency services	168 (65)	114 (88)	10 (21)	23 (49)	11 (58)	2 (29)	1 (25)	3 (43)
Primary health services	74 (29)	12 (9)	34 (72)	17 (36)	5 (26)	5 (71)	3 (75)	4 (57)
Baby clinic (hospital)	10 (4)	0	1 (2)	6 (13)	2 (11)	0	0	0
Hospital transfer	8 (3)	3 (2)	2 (4)	1 (2)	1 (5)	0	0	0
Total								
Initial	260	129 (50)	47 (18)	47 (18)	19 (7)	7 (3)	4 (2)	7 (3)
Final*		149 (57)	71 (27)	116 (45)	84 (32)	63 (24)	87 (34)	7 (3)

*Exceeds 100% because of multiple findings
Total initial and final percentages are calculated from the total number of cases, all other percentages are calculated from the initial total in that category

Table 2 *Age ranges at diagnosis of various categories of abuse*

Category	*No**	*Mean (SE) age in years*	*Range*	*Standard deviation*	*Comparison of each subset with the rest of the sample (Mann-Whitney p value)†*
Whole series	260	2·29 (0·18)	0–14	2·89	—
Non-accidental injury	149	2·48 (0·22)	0–13	2·66	+p<0 01
Growth problems	71	1·60 (0·25)	0–12	2 02	−p<0·05
Speech/developmental delay	87	2·05 (0·30)	0–13	2·50	−p<0·05
Behavioural/emotional problems	63	4·0 (0·46)	0–14	3 60	+p<0 001
Physical neglect	84	2·76 (0 36)	0–13	3·20	Not significant

*Total in number column exceeds number in sample because of multiple feature in many subjects

†Each subset is compared with the rest of the sample with the individuals in the subset removed, + or − indicates the direction each subset differs from the rest

By Mann-Whitney U test growth problems *v* behavioural/emotional problems, p<0·001; non-accidental injury *v* growth problems, p<0·05; non-accidental injury *v* behavioural problems, p<0·05 In each subset the subset being compared has been omitted where overlap occurs

(60%); neglect, 65 (77%); behaviour problems, 56 (89%); and evidence of developmental/speech delay, 83 (95%). Statistical correlation was based on presence of these features at the end of the study period.

The age distribution of the various categories is summarised in table 2.

DEVELOPMENT AND SPEECH DELAY

A total of 87 (34%) out of 260 abused or neglected children showed evidence of developmental or speech delay, or both. In four cases this was the primary diagnosis while in 83 it was an associated or subsequent finding. The association with growth failure and non-accidental injury is shown in tables 3 and 4.

Table 3 *Children with developmental/speech delay associated with growth problems and non-accidental injury*

	No (%)	*Total No (%) in series (n=260)*	*% In each subset*
Developmental/speech delay associated with	n=87		
Growth problems	38 (44)	71 (27)	54
Non-accidental injury	47 (54)	149 (57)	32
Non-accidental injury without growth problems	26 (30)	116 (45)	22
Growth problems without non-accidental injury	17 (20)	38 (45)	45
Growth problems and non-accidental injury	21 (24)	33 (13)	64

The results of χ^2 analyses of these data show that after correction for overlap among subsets, growth problems are significantly more often associated with delay than non-accidental injury but that the combination of growth problems and non-accidental injury has a higher prevalence of developmental delay than either alone.

Table 4 *Comparisons of prevalences of developmental/speech delay in children with growth problems and non-accidental injury*

	χ^2	*Odds ratio (95% confidence intervals)*	*p Value*
Remaining cases in series compared with.			
Growth problems	16 40	3 29 (1·79 to 6·05)	<0 001
Non-accidental injury	˙0 39	0 81 (0 47 to 1·42)	NS
Growth problems without non-accidental injury	1 98	1·76 (0·83 to 3 73)	NS
Non-accidental injury without growth problems	10·6*	0 39 (0 22 to 0·70)	<0·001
Growth problems and non-accidental injury	13·9	4·26 (1·87 to 9·80)	<0·001
Growth problems only compared with non-accidental injury only	6·02	2 80 (1·20 to 6·50)	<0 01
Growth problems and non-accidental injury compared with non-accidental injury without growth problems	18·3	6 06 (2·40 to 15 20)	<0·001
All growth problems compared with non-accidental injury without growth problems	17 6	3·99 (2 00 to 8 00)	<0 001

*Negative relation

EMOTIONAL AND BEHAVIOURAL PROBLEMS

Only seven children were initially found to have evidence of behaviour disturbance. Some other form of abuse or neglect had been previously noted in the remaining 56 cases. The factors associated with children showing behaviour and emotional problems are summarised in table 5. There was significantly more disturbance among children who had developmental delay and physical neglect than for the rest of the series (χ^2 15·6; p<0·001). The prevalence of disturbance in relation to age is shown in table 6.

EMOTIONAL DEPRIVATION

Evidence of deprivation was present in 47 (18%) out of the 260 children initially and rose to 116 (45%) with follow up. The highest prevalences of deprivation were seen in children who had developmental/speech delay, emotional and behaviour problems, or physical neglect (table 7) All the children initially diagnosed as being emotionally deprived subsequently developed one or more of the other features listed

Table 6 *Changes in prevalence of emotional and behavioural problems with age*

	No/No in whole series (%)
Children with emotional and behavioural problems	
≤2 years	19/147 (13)
<2–4 years	13/52 (52)
<4–6 years	12/28 (43)
<6 years	19/33 (58)

Row × column χ^2 (multiple contingency) 35·5, p<0·001, χ^2≤4 years compared with >4 years 28 8, p<0·001

Table 7 *Comparison of prevalence or deprivation in various forms of child abuse*

	χ^2	*p Value*	*Odds ratio (95% confidence intervals)*
Non-accidental injury (58/149) compared with the rest (58/111)	4·05	<0·04*	0 58 (0·34 to 0·98)
Developmental/speech delay (64/87) compared with the rest (29/173)	78 8	<0·001	13·8 (7 10 to 27·10)
Emotional behaviour problems (45/63) compared with the rest (71/197)	22·8	<0·001	4·4 (2·30 to 8·60)
Physical neglect compared with the rest (61/176)	20·6	<0·001	3·58 (2·00 to 6·40)
Growth problems (35/71) compared with the rest (81/189)	0 62	NS	1·30 (0·72 to 2 30)

In each subset, the one with which it is being compared is omitted
*Negative relation.

Table 5 *Factors associated with children showing behavioural and emotional problems (n=63)*

	No/No in each subset (%)	χ^2	*Odds ratio (95% confidence intervals)*	*p Value*
Emotional and behavioural problems associated with				
Whole series	63/260 (24)			
Non-accidental injury	35/149 (24)			
Growth problems	9/71 (13)			
Developmental/speech delay	31/87 (36)			
Physical neglect	29/84 (35)			
Non-accidental injury compared with growth problems	30/114 (26) 6/41 (15)	1 69	2 08 (0·74 to 6·14)	NS
Non-accidental injury compared with developmental/speech delay	18/102 (18) 16/48 (33)	3·7	0·43 (0 18 to 1 01)	NS
Growth problems compared with developmental/speech delay	3/38 (8) 27/59 (46)	*	—	<0·01

*Fishers's test of exact probability

RELATION OF NON-ACCIDENTAL INJURY TO OTHER FINDINGS

Sixty seven (45%) children out of 149 with non-accidental injury had neither growth problems nor were considered to have been emotionally deprived. Of these six (9%) had developmental/speech delay and five (8%) had behaviour disturbance. Of those 82 (55%) children with non-accidental injury who had either growth problems or emotional deprivation, or both, 41 (50%) showed developmental/speech delay and 30 (37%) had behaviour disturbance. The differences between the two groups was highly significant for both developmental/speech delay (χ^2 27·9, $p<0·001$) and for behaviour problems (χ^2 15·8; $p<0·001$).

Discussion

The effects of child abuse and neglect on development and behaviour have been the subject of recent concern.[1–7] Their association with poor growth is a well known phenomenon.[8] It has also been noted that abused children who failed to thrive subsequently developed 'intellectual and verbal failure to thrive' and were becoming 'problem children'.[9]

The cause of growth failure in abused and neglected children remains a matter for speculation[10] with workers dividing between those who regard it as primarily a nutritional problem[11] [12] and those who emphasise the endocrine disturbance secondary to deprivation.[13–15] In either event the presence of poor growth is very likely to be accompanied by a disorganised, disrupted, and deprived family environment that would help to explain the unfavourable prognosis for intellectual and behavioural development.[16] [17] Underlying poor nutrition may be common to both hypotheses.[7]

Although some catch up in physical growth tends to occur with time,[1] it may not allow for the attainment of full genetic potential for size and may not be associated with full recovery of intellectual potential.[8] Some children may, however, be very resilient to adversity and do well despite their background of abuse.[19]

Some authors have defined the underlying cause of growth failure as a combination of absence of proper maternal attachment with parental anger, hostility, and hate,[14] a combination likely to result in developmental delay and behaviour disturbance. Our data show that such secondary features are common and illustrate the importance of careful paediatric evaluation of all abused children. It may be that these phenomena stem from events at, or soon after birth of the child leading to a disturbed child–parent relationship.[20] In view of the fact that in an appreciable proportion of children with growth failure no cause, either organic or psychological can be detected.[2] psychosocial growth failure should not be diagnosed without additional evidence of poor parenting or the consequences of abuse or neglect. Physical neglect appears to be a useful 'marker' for emotional deprivation and its consequences.

The prevalence of developmental/speech delay in the cohort of abused and neglected children reported here is high (34%), higher than would be expected in the general population. It is likely that the degree of delay exhibited by these children is in excess of what might be expected for any equivalent group but in the absence of population data this cannot be certain. The comparisons in this study are relative and indicate that problems of growth rather than physical injury are more likely to be associated with delay. This is not surprising when it is recognised that whereas physical injury can be the result of a relatively short term maladjustment, growth problems indicate much more long standing difficulties. This difference also indicates that delay in speech and development is more than merely an epiphenomenon in the child abuse spectrum.[22–24]

The appreciably higher age distribution of the injured children is to some extent accounted for by the 'over-chastisement' of older children. In a proportion of these this appears to stem from intolerable disturbed behaviour due to neglectful or abusive parenting in the past. The older abused children thus fall into two categories: those in whom there has been a long term history of mismanagement and those in whom the abuse—usually non-accidental injury—is the result of recent change—that is, a new step father or cohabitee or some negative change in family circumstances. The former are likely to show the emotional and developmental consequences of long standing abuse and neglect.

Nineteen (58%) of the 33 children over 6 years of age had behaviour or emotional problems. Nearly half the children with these problems had developmental/speech difficulties in contrast with less than one third of the series as a whole. Relatively few of the younger children with growth or development problems showed behaviour difficulties probably because of their age.

The children who showed developmental delay, and in the older children disturbed behaviour, were most likely to have been emotionally deprived. The higher prevalence of development and behaviour problems in non-accidentally injured children who had either shown growth problems or evidence of emotional deprivation also points to the effect of more chronic poor parental practice on abused children. The prevalence of emotional and behavioural problems would be expected to rise as the infants and toddlers in the series reach school age. Given as overall prevalence of 24%, which rises steadily with age, these children pose major problems despite all efforts at rehabilitation. Many older abused children appear to emerge from their experience with seriously damaged personalities despite active intervention. A pattern of abuse manifesting as injury with growth problems and developmental delay may not be readily amenable to rehabilitation as these are the children most likely to develop behaviour problems and learning difficulty. It is disturbing to note the increasing proportion of children with emerging personality problems with increasing age (table 6).

The virtual absence of children with sexual abuse in this series stems from two factors. In the first instance, most of the cases come from a period where sexual abuse had not gained its current importance. Secondly, during the latter few years of the study most children who were considered to be primarily sexually abused were not included unless there was evidence of other forms of abuse, as this study was not primarily concerned with sexual abuse. It is possible that at least some children in the series also suffered sexual abuse that was not diagnosed.

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Aetiology of mild mental retardation

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SUMMARY A clinical and family study was carried out in 169 children attending schools for the mildly mentally retarded in Southampton to assess the prevalence of recognised medical risk factors; 71 children (42%) had such risk factors. These were prenatal in 22, perinatal in 41, and postnatal in eight. Risk factors of possible, but less certain, significance were found in a further 63 children (37%). In 86 families (51%) there was a history of serious educational problems in both parents. The prevalence of both types of risk factor was higher in the children whose parents had no educational problems. There were, however, 25 children (15%) whose parents had no history of educational problems and in whom medical risk factors were either absent or minimal.

The traditional view that mild mental retardation is largely caused by polygenic and sociocultural influences has been challenged by recent studies.[1–3] Increasing ability to identify genetic syndromes, chromosome abnormalities, and biochemical defects associated with mental retardation, has extended the scope of diagnosis and the possibility of attributing mental retardation to a specific cause. We therefore undertook a study of children attending schools for the mildly mentally retarded to assess the contribution of medical, and especially genetic, factors of recognised aetiological importance. Medical factors of possible but not fully established relevance were also recorded. We hoped to assess the extent to which mild mental retardation in the local population might be reduced by early diagnosis followed by treatment, genetic counselling, or prenatal diagnosis.

Children identified as having delayed development during preschool years are usually seen by a paediatrician for assessment, but mild mental retardation may not be apparent until after a period in a normal school. Children referred for special education at this stage are not usually referred for a paediatric opinion unless there is a specific indication. We hoped that this study would provide guidelines for the medical investigation of children attending schools for the mildly mentally retarded. Non-medical factors such as parental education and home environment are considered briefly here, but are the subject of another report.[4]

Patients and methods

Schools for the mildly mentally retarded provide education for children with learning difficulties; there are separate schools for children with physical handicaps. Southampton is well provided with facilities for mildly mentally retarded children. Referral requires parental approval but is otherwise unrestricted. The survey was carried out before the 1983 Education Act which encourages integration of 'less able' pupils into normal schools, and hence children were more readily referred than at present.

The study population was drawn from children aged 7–11 years attending the three Southampton schools that provide education for mildly mentally retarded children. At the time of the study the total school population aged 7–11 years was 11 921, of whom 229 (2%) attended schools for the mildly mentally retarded. One hundred and sixty nine children (93 boys and 79 girls) were included in the study. The parents of 31 children declined to take part and the parents of 19 did not actively refuse, but did not cooperate. Six children who were in foster homes and four who left school in the course of the study were also excluded.

Children referred to schools for the mildly mentally retarded do not always have their intelligence quotient (IQ) tested beforehand. Referral is usually because of an inability to cope with normal education, and IQ assessment by an educational psychologist is secondary. Eighty nine (53%) children in the survey had IQs within the accepted range of mild mental retardation (IQ 50–70).[5] Seventy five (44%) were of borderline intelligence (IQ 71–85). Five (3%) had not had a formal test. The study was therefore not confined to children with mild mental retardation, but included children of borderline intelligence whose learning problems had been sufficient to merit referral to a special school.

With the cooperation of head teachers and with the knowledge of family doctors, parents of children attending the schools were invited by letter to take part in the survey. Those who agreed were visited at home where a family history was taken and parents were asked about their own medical and educational backgrounds. They were asked for details of pregnancies, and the births, early development, and education of all their children. Blood and urine specimens were taken from the mothers, and written permission was obtained for study children to be seen and tested. School medical records and hospital records were checked for information about the children's medical histories.

At school each study child had a detailed clinical examination that included measurements of height, weight, and cranial circumference, and inspection for minor malformations including abnormal skull shape, unusual facies, abnormal ears, hypertelorism, epicanthic folds, high palate, asymmetric chest, wide spaced nipples, clinodactyly, single palmar crease, abnormal finger creases, minor malformations of fingers and toes, and abnormal dermatoglyphics. Coordination was tested by hand tapping, finger/thumb and finger/nose apposition, heel/toe walking, and hopping. The child's performance in each test was rated as satisfactory or poor. Poor performance in two or more tests indicated incoordination. The same series of measurements, examination for minor malformations, and coordination tests was carried out on 55 children in the same age range attending normal schools. Blood and urine samples were taken from the study children. All urine samples were screened by standard methods for glucose, protein, blood, ketones, cysteine, cystine, and homocystine. Quantitative amino acid analysis was done on mothers' blood samples with a Rank-Hilger-Chromaspeck amino acid analyser. Blood spot screening for hypothyroidism and phenylketonuria, and chromosome analysis including examination for the fragile (X) chromosome, were done on children's blood samples.

Table 1 *Medical features of probable aetiological importance in 71 mildly mentally retarded children*

Aetiological feature	*No of children*
Prenatal	
Chromosome abnormality	8
Malformation of the central nervous system	5
Infection	2
Sotos' syndrome	1
Aarskog's syndrome	1
Rubenstein-Taybi syndrome	1
Cohen's syndrome	1
Prader-Willi syndrome	1
Alcohol fetopathy	1
Inborn error of metabolism	1
Perinatal:	
Twitching or cyanosis during first week	16*
Apgar score <7 at 5 minutes	16†
Fetal distress	10‡
Blue or limp at birth	4
Postnatal:	
Infection of the central nervous sytem	3
Apnoea	2
Status epilepticus	1
Intracranial haemorrhage	1
Severe pertussis	1

*Includes two with prenatal signs; †includes three with prenatal features, ‡diagnosed by obstetrician.

Perinatal factors in index children with no major prenatal or postnatal factors were compared with those of their unaffected siblings (attending normal schools) who acted as paired controls. The control sibling was defined as the one nearest in age to the index patient, and those index patients with no unaffected siblings were left out of the comparison.

Postnatal events were considered significant if the child had been developing normally before the event, but showed developmental delay thereafter.

Results

KNOWN RISK FACTORS

Medical features that probably contributed to the referral were identified in 71 of 169 children (42%). (table 1). Only five children had more than one such feature, and all of these had a combination of prenatal and perinatal features.

Prenatal features

Chromosome abnormalities were present in eight of 22 children with prenatal features. These have been described elsewhere.[6] Three children—two girls with Down's syndrome, and a boy with karyotype 46,XY,14q+—were known to have a chromosome abnormality before the survey. The others included three boys with sex chromosome aneuploidy—47,XXY (2), and 48,XXYY (1), one girl with an autosomal deletion—46,XX,del(15)(q11·2;q13·1), and one girl with an X-autosome translocation, 46,X,t(X;19). None of these five children had obvious dysmorphic features. Mothers of four children—the two with Down's syndrome, one boy with Klinefelter's syndrome, and the girl with karyotype 46,XX,del(15)—were aged 38 years or over when the children were born.

Two children had 'Mendelian' syndromes; one boy had Sotos' syndrome and his mother also had features suggestive of the syndrome. One boy had

Aarskog's syndrome. There was no family history of retardation, but his mother and grandmother were of short stature and had ptosis. Three children had 'non-Mendelian' syndromes associated with mental retardation. One boy had Rubinstein-Taybi syndrome, which had been identified at birth. Two children were identified in the survey; one girl had Cohen's syndrome, and one had Prader-Willi syndrome, without a demonstrable chromosome abnormality. Of three girls with microcephaly, one had minor dysmorphic features that did not fit into any recognised syndrome; the other two had no associated physical features. All three had pronounced incoordination. Two boys had hydrocephalus, one of which had been diagnosed and treated surgically when he was referred for a clicking hip at the age of 4 weeks. The other, born at 34 weeks' gestation, had birth asphyxia and a stormy neonatal course. Hydrocephalus, noted at 7 weeks of age, was not treated surgically.

Two children had had prenatal infections. Toxoplasmosis was diagnosed at the age of 9 months in one child who had severe retinal scarring and intracranial calcification. The mother of one boy had acquired syphilis in the first trimester, and he had antibodies present at birth. One child, with an alcoholic mother, had features of the fetal alcohol syndrome. One other mother admitted to heavy drinking in pregnancy; her child had an X-autosome translocation but no features of fetal alcohol syndrome. Congenital adrenal hyperplasia had been diagnosed in a child at the age of 5 days. This led to a crisis seven weeks later with fitting, opisthotonos, and subsequent facial palsy. The investigations carried out on urine and blood samples did not show any biochemical defects in mothers or children, nor any hypothyroidism in the children.

Perinatal features

Nineteen children had been born outside the Southampton district; birth records for nine could not be traced, but the mothers gave no history of perinatal problems. Six children had been born at home: one was admitted to hospital blue and limp shortly after birth, but there was no history of perinatal stress in the other five. Thirty nine children had been born in small peripheral hospitals where Apgar scores were not routinely recorded. Three of these children who were blue and limp at birth and were transferred to special care units have been included in the group with recognised perinatal stress. A history of perinatal stress was the only recognisable risk factor in 41 children. Five children with an adverse perinatal history also had a significant prenatal feature—two children had chromosome abnormalities (47,XXY, 46,XX,del(15)), and one boy with hydrocephalus had low Apgar scores; the other hydrocephalic boy and the child with congenital adrenal hyperplasia had recorded neonatal twitching.

One hundred and twenty study children with no recognisable prenatal or postnatal risk factors had siblings receiving normal schooling. The perinatal features of the study and control groups are shown in table 2. Recordings of fetal distress or low Apgar scores were less than half as common in the control as in the study group. No child in the control group had recorded neonatal twitching or cyanosis. Overall, the incidence of adverse perinatal factors was significantly less in the control group ($p<0.001$).

Table 2 *Perinatal features in 120 mildly mentally retarded children and paired siblings receiving normal education who acted as controls*

	No of study children	*No of normal children*
No adverse feature	87	111
Adverse features:		
Fetal distress	9	3
Apgar score <7 at 5 minutes	11	5
Blue or limp at birth	2	1
Twitching or cyanosis during first week	11	0

Postnatal features

Two children had had meningitis, aged 6 and 9 weeks, respectively, and one girl had had encephalitis when she was 3 years old. One boy found cold and limp in his cot when 3 weeks old, and another found apparently lifeless in his pram at 6 months were regarded as 'rescued cot deaths'. Both these children had behaviour problems. One boy, when aged 18 months developed status epilepticus which took three to four days to come under control; he also had a behaviour disorder. One child developed bilateral subdural haematomas after a non-accidental injury, and she had a residual hemiparesis. The last child in this group was developing normally until he had prolonged pertussis at the age of 2 years. He has since been physically as well as mentally delayed, with small stature and retarded bone age.

POSSIBLE RISK FACTORS

One hundred and six study children had in their history or examination medical features of possible relevance but with no established link with retardation. Forty three of these children also had recognised risk factors. Of 63 children with risk factors of only possible relevance, 37 had just one feature, and 26 more than one (table 3).

Three children had been born to mothers with type I diabetes and in all three this was the only medical factor noted. Insulin control was reasonable—none of the mothers had 'brittle' diabetes. One of the children weighed 4770 g (>97th centile) at birth but there were no problems at delivery; the other two children had birth weights within normal limits. Four children—all boys—had major malformations not affecting the central nervous system; three had cleft lip and palate, one of whom also had Poland's anomaly. The fourth child had a ventricular septal defect that was successfully repaired when he was 2 years old.

Twenty one survey children were born at or before 36 weeks' gestation, but in none was this the sole feature. Thirty survey children (18%) had heights on or below the third centile. Ten of these children had no other medical feature. Four of 55 control children (7%) had this degree of short stature. Ten children (6%) had cranial circumferences on or above the 97th centile. This was the sole medical finding in four. Two control children (4%) had this degree of macrocephaly. Twenty one children (12%) had severe behaviour problems, all but two of whom had other medical features. Of the

Table 3 *Medical features with no well established link with mental retardation in 106 mildly mentally retarded children*

Feature	*No of times each feature present (n=106)*	*No of children in whom this was sole medical feature (n=37)*	*No of times this feature was accompanied by a known risk factor (n=43)*	*No of times this feature was accompanied by one or more other feature (n=26)*	
				One	*More than one*
Prenatal:					
Twinning	9	0	2	2	5
Chromosome translocation	1	0	0	0	1
Maternal diabetes	3	3	0	0	0
Maternal drug taking	6	0	2	2	2
Maternal operation	1	0	0	0	1
Maternal injury	2	1	0	1	0
Threatened abortion	8	1	4	2	1
Hyperemesis	14	2	7	3	2
Maternal toxaemia	14	4	9	0	1
Maternal anaemia	5	0	1	0	4
Small for gestational age	11	1	5	2	3
Major malformation	4	1	2	0	1
Perinatal					
Gestation <37 weeks	21	0	11	2	8
Antepartum bleeding	4	1	0	1	2
Rapid delivery	3	1	1	0	1
Neonatal jaundice	10	0	7	0	3
Excessive weight loss	1	0	0	0	1
Postnatal					
Severe malnutrition	2	0	1	0	1
Immunisation reaction	1	0	0	0	1
Head injury	2	0	0	0	2
Other (timing uncertain)					
Height on or below 3rd centile	30	10	8	3	9
Head circumference on or above 97th centile	10	4	3	2	1
Epilepsy	9	0	5	2	2
Behaviour problems	21	2	13	2	4
Three or more minor malformations	10	2	3	2	3
Incoordination	42	4	27	4	7

children with IQs of more than 70, eight (11%) had behaviour problems, compared with 11 (12%) of those with IQs of less than 70 (two children were not tested).

Ten survey children (6%) had three or more dysmorphic features unrelated to chromosome abnormalities or recognised syndromes. In the control group the corresponding frequency was two of 55 (4%).

Forty two children (25%) had incoordination, four of whom had no other risk factors identified. Twenty seven had known risk factors: chromosome abnormality (n=5), a recognised syndrome (n=2), microcephaly (n=3), congenital adrenal hyperplasia (n=1), perinatal stress (n=13), meningitis (n=1), head injury (n=1), and status epilepticus (n=1). Incoordination was not a feature in the two boys with XXY, the girl with the X-autosome translocation, and two of the three children who had infections of the central nervous system. Four of the control children (7%) had incoordination.

Parental education

Parental educational problems were defined as attendance by the parent at a school for the mildly mentally retarded, or an admission of illiteracy or semiliteracy. For a child to be designated as having parents with educational problems, such a history was required from both parents. There was a history of educational problems in the parents of 86 children. Table 4 shows the incidence of parental education problems in children with known risk factors, those with a single possible risk factor, those with two or more possible risk factors, and those in whom no medical features were identified. The percentage of parents with educational problems was lowest in the first of these groups (39%), and highest in the last (77%). Eight children with parents of average or superior education had no medical features identified in their history or examination, and a further 17 had just one possible risk factor.

Table 4 *Medical features and parental education of 169 mildly mentally retarded children*

	No of children	*No (%) of children of whom both parents had educational problems*
Features of known aetiological importance (with or without other possible risk factors)	71	28 (39)
Two or more possible risk factors	26	11 (42)
One possible risk factor	37	20 (54)
No medical features	35	27 (77)
Total	169	86 (51)

Discussion

The attribution of mild mental retardation to medical factors is fraught with difficulties. There is no good working definition of the phenotype, many of the relevant medical factors are open to subjective interpretation, and control data are inadequate, especially in the rapidly changing specialty of perinatal care. Despite these difficulties it is an area requiring medical study. Parents generally appreciate a medical 'label', and genetic counselling may be important. Recent study of the fragile X syndrome[7 8] has shown that medical factors are not confined to severely retarded children. It has often been assumed that most mild retardation is multifactorial. If the distribution of IQs was normal, 3% of the population could be expected to have IQs of less than 70. We found that 2% of the Southampton schoolchildren aged 7–11 were attending schools for the mildly mentally retarded at the time of our survey, but only half of these were in the IQ range 50–70. The factors apart from IQ that influence referral for this type of special education are not clear. Parental approval is required, and referral must be to some extent dependent on facilities for remedial education available in normal schools. We expected (but did not find) that children with IQs of over 70 would be more likely to have behaviour problems. Selection could bias the study sample either towards or away from identifiable medical causes.

Over a quarter of the children in the schools for the mildly mentally retarded were not included in the survey. Parents of 31 children actively declined to take part and although no reason for refusal was sought two explained that this was because their children had already been thoroughly investigated, and a further nine stated that they did not wish to submit their children or themselves to venepuncture. Nineteen families did not respond and were not available for two home visits at prearranged times. Sociocultural problems may be important in these families, and their exclusion could have biased the population sample.

The risk factors shown in table 1 are plausible explanations of mental retardation, although some doubt must remain about the individual importance of the perinatal features. Comparison with paired sibling controls showed a significant excess of perinatal problems in the index patients. Some of these are, however, subjective or poorly standardised, and there is always the possibility that perinatal difficulties are secondary. Other factors, including the child's original potential, may reduce or enhance the consequences of early brain damage. Bearing in mind these caveats, perinatal events of the type we have reported must be considered as having potential aetiological significance.[9 10]

Medical factors having a probable association with mild mental retardation were identified in 71 of these children (42%). Hagberg[1] in a study of 91 Swedish children with IQs of 50–70, found similar factors in 43%. From the results of our survey we believe that reduction of the genetic contribution to mild mental retardation by appropriate genetic counselling would not be feasible. The eight chromosomal abnormalities had all arisen de novo, though four of the mothers were over 35 years when the children were born. All children in the survey were born before August 1976. More recently their mothers might have been offered amniocentesis. Three other children had prenatal genetic defects (Sotos' syndrome, Aarskog's syndrome, and congenital adrenal hypoplasia), but in all three the genetic defects became apparent only after the birth of the children. Alcohol fetopathy was found in only one child in contrast with the Swedish study[1] in which 8% of mildly retarded children had the fetal alcohol syndrome.

We have not so far been able to account for the lack of fragile (X) chromosome cases in our sample. Extrapolating from the data of Webb *et al*[7] we should have expected five affected boys in our age group in Southampton, two or three of whom might have been at schools for the mildly mentally retarded, plus perhaps four or five affected girls. The relevant cytogenetic techniques leave scope for variability, but the laboratory did make this diagnosis on samples from other sources during the period of the survey.

Though no firm conclusions could be drawn from the group of 63 children who had possible risk factors alone, certain points emerged. Maternal diabetes was the sole medical feature in three children. Children born to diabetic mothers are at increased risk of physical abnormalities[11] but we are not aware of any previous association with mental retardation. One of these children, who had parents of normal intelligence, had a brother who was also retarded. Thirty children (18%) were of small stature. In two, this could be related to medical conditions (fetal alcohol syndrome and severe pertussis), but in 28 children there was no obvious cause. In 10 children small stature was the only medical feature noted. The association beween small stature and mild mental retardation is not clear, but there may be an interaction between the behavioural attributes of the parents and the child.[12] Incoordination, which featured in 42 children (25%) was associated with known risk factors in 27 (13 with perinatal stress). In contrast, Hagberg[1] found that 43% of mildly retarded children had a neurological abnormality, but does not give details of the method of assessment used.

Children in all the aetiological groups had parents who had had educational problems, but the proportion was highest (77%) in 27 children with no recognised medical risk factors; in 37 children with just one possible risk factor, parents of 20 had had educational problems. Polygenic factors may contribute appreciably to the mental retardation in these two groups of children, but similar findings could be produced by as yet undetected major familial factors such as single gene defects.

We found no previously unrecognised errors of metabolism in the mothers or children in the survey, hence routine biochemical testing would not seem appropriate in the aetiological investigation of children at these special schools. We recommend careful physical examination of the children by school medical officers, looking especially for minor dysmorphic features. Referral to a paediatrician or geneticist should be considered if three or more dysmorphic features are found, or if a genetic syndrome is suspected. We recommend chromosome analysis for all mildly mentally retarded children irrespective of whether there are any dysmorphic features. Finally, in assessing the children account should be taken of the level of parental intelligence and of any possible contributory features in their history, but in some children no cause for the retardation will be found. There were eight children in this survey who had parents of normal intelligence and no medical features identified, and a further 17 (again with normal parents) who had just one feature of uncertain relevance to account for their retardation. It was beyond the scope of this study to investigate these children further, but identification of children with idiopathic mild mental retardation and their further neurological investigation might be of value.

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Hyperventilation in the awake state: potentially treatable component of Rett syndrome

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SUMMARY Hyperventilation, which occurs in some patients with severe mental handicap, is a prominent feature in the histories of most girls with Rett syndrome but its mechanism and effects have not been established. Respiratory function was therefore studied in 18 patients with Rett syndrome and 23 healthy controls. Ten of the patients (56%), but none of the controls, hyperventilated only when awake, and began doing so after a period of normal breathing without hypoxaemia. After hyperventilation was established it was interspersed with prolonged periods of apnoea (over 19 seconds) accompanied by Valsalva manoeuvres. Hypoxaemia (<90%) occurred in 47% of these periods of apnoea and five (50%) of the patients had oxygen saturation values of under 50%. During hyperventilation severe hypocapnia developed in every patient, and recorded arterial pH measurements ranged from 7·47 to 7·60. A further four patients (22%) did not hyperventilate, but had clear histories of hyperventilation when younger. All had frequent apnoeic pauses accompanied by Valsalva manoeuvres. The remaining four girls (22%) neither hyperventilated nor gave a clear history of doing so. Three had occasional apnoeic pauses associated with the Valsalva manoeuvres. All but one of the 18 patients had increased quantities of periodic apnoea compared with the control subjects.

The hypocapnic alkalaemia and hypoxaemia resulting from hyperventilation may contribute to the cerebral impairment in Rett syndrome. Since the hyperventilation is 'primary', and not secondary to preceding apnoea, it is potentially treatable. Further studies will determine if treatment is practical and of benefit.

Rett syndrome is a comparatively common cause of severe mental and physical handicap. The syndrome was first described in 1966,[1] and only affects girls, the estimated prevalence is 0·8/10 000 girls up to the age of 14 years.[2 3]

Hyperventilation is a well known clinical characteristic of some patients with Rett syndrome, and there has been research into the causes of the prolonged apnoeic episodes and hypoxaemia that are also seen in these patients.[4] A study by Glaze *et al* has suggested that hyperventilation is a compensatory response to periods of disorganised breathing and hypoxaemia.[5] Our findings do not confirm these results, but show that hyperventilation is the primary respiratory problem and that the prolonged apnoea and hypoxaemia are secondary components. In this paper we present data on the prevalence of hyperventilation and its effects on respiratory function, heart rate, and plasma biochemistry.

Patients and methods

The control group comprised eight girls and 10 boys aged between 4 and 6 years who had been originally and randomly recruited at birth as part of a large prospective study of respiratory function,[6] and four girls and one boy aged between 6 and 15 years who were recruited from schools in the Doncaster area. All were healthy and were studied at home.

Eighteen girls between 6 and 17 years with Rett syndrome were studied. The clinical characteristics of 14 of them have previously been reported by Kerr and Stephenson[2 3]; four were new cases. Because no organic marker has yet been described for Rett syndrome, it has to be distinguished on clinical grounds alone. To allow valid comparisons among cases from different centres we have defined precisely what we mean by 'classic Rett syndrome' and have indicated any cases in the series who do not have all the classic features.[7]

In this study a classic case of Rett syndrome met all the following criteria:

(1) There were no serious complications during pregnancy, birth, or the neonatal period, and the girl conformed to accepted standards for psychomotor development during the first 4 months, (2) the occipitofrontal head circumference was within or close to the normal range at birth and increased at a normal rate for at least the first four months, but suboptimal growth occurred later in childhood; (3) there was subtle evidence of slowing in psychomotor development in the first year, failure to use the hands properly after the first 12 months and failure to develop speech beyond single utterances; (4) there was otherwise unexplained loss of skills in the use of hands and speech between the ages of nine and 30 months associated with social withdrawal and deterioration in non-verbal communication; and (5) characteristic repetitive hand movements developed, consisting of simple hand wringing or squeezing, clapping or tapping, and washing or rubbing. Following this regression, lack of postural control developed, often with involuntary movements, the use of hands deteriorated and became uncoordinated, and the child had no useful speech although non-verbal communication improved.

In addition the child had a profound and essentially static mental handicap with no other obvious cause, and was prone to sudden spells of agitated behaviour including panic, laughter, or altered respiration. There were no dysmorphic features.

Other features of Rett syndrome are cold, small, and slim hands and feet, epileptic seizures and nonepileptic absences often preceded by hyperventilation, gaseous abdominal distension, wasting, progressively increasing tone (especially in the lower limbs), progressive scoliosis, and deformity of the feet and ankles.

Only four of our 18 patients had atypical features; case 9, aged 6 years, had a greater than usual (although still poor) ability to speak and use her hands. For the last three years she had undergone a programme of stimulation teaching, and exercises for five hours a day, six days a week. The mother of case 10 had a history of infertility, and had had hormone treatment for a threatened abortion at 11 weeks' gestation. Polyhydramnios was present in the third trimester. In cases 15 and 18, stereotypic hand movements had virtually disappeared by the time of this study.

The control subjects underwent single long term tape recordings (awake and asleep) of oxygen saturation, arterial pulse waveforms, expired carbon dioxide, and abdominal breathing movements using the equipment described below (mean duration 9·7 hours, range 6–12·5).

To evaluate respiratory function in the 18 patients with Rett syndrome, recordings were made of various signals in different combinations with an FM tape recorder (Racal Store 4); these were made while subjects were awake in all cases, and overnight in 11. When more than four signals were required a single channel multiplexer (Medical Physics, Sheffield University) was used (frequency response DC to 30Hz/channel).

Expired carbon dioxide concentrations were recorded from a constantly sampling infrared analyser (Engstrom Eliza) either from a face mask or from a mouth probe held by an observer (median total response time 2·5 seconds, sampling rate 100 ml/minute). During sleep, expired carbon dioxide was measured from just inside one of the external nares using a fine cannula taped on to the upper lip. Only expired carbon dioxide signals showing adequate plateau formation were analysed. Transcutaneous carbon dioxide measurements were recorded by an electrochemical sensor (Hewlett Packard 78834A), which was heated to 42°C. Constants (according to the method of Hazinski and Severinghaus[8]) were applied to compensate for increased skin temperature and for skin carbon dioxide production (gain 0·79, offset −3 mm Hg). The sensor was taped on to the skin of the upper chest wall.

Beat to beat arterial oxygen saturation,[9] the arterial pulse waveforms from which this was calculated, and an electrocardiogram were obtained from a modified pulse oximeter (Nellcor Respox 2). The oxygen sensor was placed on the toe and electrocardiographic electrodes in the lead II position. Breathing movements were detected in all patients with Rett syndrome using respiratory inductance plethysmography (Respitrace, Studley Data Systems), either from a vest (P K Morgan) encompassing the whole of the chest wall or from two separate bands placed at the levels of the nipples and umbilicus. In two cases abdominal breathing movements were also detected from a pressure capsule transducer (Graseby, MR10). In 10 of the 23 controls, breathing movements were recorded from a pressure capsule alone and in 13 from both pressure capsule and inductance plethysmography. Recordings of airflow integrated to volume change were obtained from a close fitting face mask and a Fleisch size 2 pneumotachograph (Spectramed). Calibration signals of 60 ml were obtained using a purpose built syringe.

Six channels of electroencephalography, one channel of electro-oculography, and one channel of electrocardiography were recorded onto a battery operated cassette tape recorder (Medilog 9000, Oxford Medical Systems) with pre-amplifiers on a collar placed around the neck. During daytime recordings these signals were incorporated onto a video tape and video monitor (the Quarrier's system),[10] and time linkages were synchronised between the video recordings and the respiratory physiology data on the FM tape recorder. Numerical and oscilloscopic representations of the respiratory data were also recorded on video film. Tape recordings of the respiratory physiological parameters were printed out using an eight channel ink jet chart recorder (Siemens EEG 8). Standard recordings of the electrocardiogram were made on eight patients using a Cambridge VS-550 ECG recorder.

Single radial arterial 'stab' samples for blood gas analysis were taken and analysed during periods of hyperventilation in children showing abnormally reduced concentrations of transcutaneous or end tidal carbon dioxide, or both. In three such patients samples were not obtained. In one (case 8) the parents refused consent. In the second (case 3) bronchospasm was present as well as large amplitude and rapid breathing, but end tidal and transcutaneous carbon dioxide were not reduced. In the third (case 10) a sample could not be obtained during the hyperventilation. Plasma concentrations of sodium, potassium, chloride, magnesium, phosphate, ionised calcium, and lactate were also measured.

Periods of hyperventilation were diagnosed when plateau values of end tidal carbon dioxide fell below 3·0 volume %, amplitude of breathing movements increased, and trancutaneous carbon dioxide fell below 30 mm Hg. The durations of all apnoeic pauses were measured in the controls the longest of which was 19 seconds. All pauses over 19 seconds occurring in the 18 patients with Rett syndrome were measured together with their effects on oxygen saturation.

Periodic apnoea was defined according to Richards *et al*[11] and measured in cases and controls. Thus a cycle of periodic apnoea consisted of a group of 1–19 breaths followed by an apnoeic pause of ≥ 4·0 seconds. Each cycle was preceded by a similar pause or by a cycle of periodic apnoea. A minimum of two cycles of periodic apnoea was required to complete an episode of periodic apnoea.

Results

Analysis of the tape recordings from the 23 controls showed no evidence of hyperventilation. Apnoeic pauses up to 19 seconds in duration were identified

Table 1 *Clinical details of patients with Rett syndrome*

Case No	*Age (years)*	*Occipitofrontal head circumference (%)*	*Motor seizures*	*Scoliosis*	*Foot deformity*	*Gaseous abdominal distension*	*Past history of hyperventilation*	*Current treatment*
Group 1:								
1	6	3–10	Yes	Yes	Yes	No	Yes	Carbemazepine
2	12	3–10	Yes	Yes	Yes	Yes	Yes	Carbemazepine
3	11	<3	No	Yes	Yes	Yes	Yes	Salbutamol
4	10	<<3	Yes	Yes	Yes	Yes	Yes	Sodium valproate
5	7	10	No	No	No	Yes	Yes	None
6	16	<<<3	No	Yes	Yes	Yes	Yes	None
7	7	<3	Yes	Yes	No	Yes	Yes	Clonazepam, carbemazepine
8	12	<3	Yes	Yes	Yes	Yes	Yes	Carbemazepine
9*	6	10–25	Yes	No	No	No	Yes	Prednisolone
10*	6	3	Yes	Yes	Yes	Yes	Yes	Carbemazepine
Group 2:								
11	17	25	Yes	No	Yes	Yes	Yes	Carbemazepine
12	14	<3	No	Yes	Yes	Yes	Yes	None
13	16	3	Yes	No	Yes	Yes	Yes	Sodium valproate
14	13	<<3	Yes	Yes	Yes	Yes	Yes	Sodium valproate
Group 3:								
15*	6	25–50	Yes	Yes	Yes	No	No	Carbemazepine
16	7	<3	Yes	Yes	Yes	Yes	No	Sodium valproate, trimeprazine tartrate
17	14	<<3	No	Yes	No	Yes	No	None
18*	6	<3	Yes	Yes	Yes	No	No	Clonazepam

*Atypical features present

Table 2 *Selected physiological data on 18 patients with Rett syndrome*

Measurement	*Case No*								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Duration of recording (hours)	14·3*	13·2*	12·9*	13·2*	13·8*	11·5*	14·7*	0·9	16·9*
Lowest values when awake:									
Transcutaneous carbon dioxide (mm Hg)	24	26	32	18	13	20	8	21	18
End tidal carbon dioxide (volume %)	2·2	2·2	4·2	2·1	1·4	2·0	1·6	2·4	1·8
Average values when asleep									
Transcutaneous carbon dioxide (mm Hg)	52	59	53	NR	37	32	38	NR	51
End tidal carbon dioxide (volume %)	5·4	7·2	4·6	5·8	4·2	4·0	4·8	NR	4·8
Longest apnoeic pause when awake	49	98	27	125	74	43	34	24	60
Lowest oxygen saturation when awake (%) (below 50% oximeter inaccurate)	60	<50	92	<50	<50	66	70	92	<50
Valsalva manoeuvres	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Periodic apnoea* (asleep) (minutes/hour)	13·5	17·8	11·3	5.6	1·7	13·8	17·0	56·1	1·7
QTc (second)	0·44	0·40	NR	0·45	0·41	0·42	0·45	NR	0·43

*Both day and overnight recordings; NR=not recorded

Table 3 *Selected biochemical data on eight of 18 patients with Rett syndrome*

Measurement	*Case No*								*Normal range*
	1	*2*	*4*	*5*	*6*	*7*	*9*	*10*	
Plasma concentrations (mmol/l									
Chloride	109	110	NS	110	109	110	105	NS	92–109
Ionised calcium	1·13	1·[illegible]5	0·67	NM	1·24	1·26	1·24	1·19	1·19–1·31
Phosphate	1·6	1·[illegible]	1·7	1·4	1·5	1·6	1·9	1·8	0·7–1·4
Lactate	2·1	1·[illegible]	2·5	3·4	1·1	2·0	2·2	1·8	0·7–1·8
*Arterial:									
pH	7·48	7·[illegible]1	7·60	7·59	7·47	7·49	7·55	NS	7·35–7·45
Bicarbonate (mmol/l)	17	22	15	13	18	20	21	NS	22–26
Carbon dioxide (mm Hg)	30	24	16	13	25	23	22	NS	35–45 mm Hg
Base excess	−1·0	−0·9	−1·5	−4·1	−2·8	−2·4	0·5	NS	−2·0–+2·0 mmol/l

*Samples taken during hyperventilation, NS=not sampled; plasma concentrations of potassium, sodium, and magnesium were all normal

(range of longest pause/recording 8–19 seconds, median 14) but these pauses were not accompanied by Valsalva manoeuvres.[12]

The patients were divided into three groups according to the results of their recordings and the clinical histories (table 1).

GROUP 1 (CASES 1–10)

There were 10 patients in group 1, with an average age of 9·3 years. When awake they all had long periods of hyperventilation. Table 2 shows the severity of their hypocapnia with transcutaneous carbon dioxide values reduced to 8 mm Hg and end tidal carbon dioxide values reduced to 1·4 volume % (control values 4·6 to 5·3 volume %). All seven of those from whom arterial blood samples were taken had respiratory alkalaemia (highest pH 7·60, table 3). When asleep none of the 10 patients had hyperventilation (end tidal carbon dioxide values were 4·0 to 7·2 volume %, control values 5·2 to 6·4 volume %) (table 2, fig 1).

During periods of hyperventilation the children seemed agitated with increased hand movements, dilated pupils, increased heart rates, rocking body movements, and increased muscle tone. They breathed through wide open mouths, ribcage excursions were greater than abdominal excursions, and accessory muscles of respiration were used. In some hyperventilation occurred almost continuously while they were awake, and in others it was interrupted by periods of normal breathing. During these latter periods the children remained awake but slightly drowsy. In some cases hyperventilation was clinically obvious. In others (for example case 4) it was only indicated by end tidal and transcutaneous carbon dioxide measurements. Though case 3 had

Table 2 *Continued*

10	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*Range in 18 controls*
17 1*	10·4*	0 6	0 5	0 4	14·7*	1·5	0·4	0 5	6·0 to 12 5
13	NR	42	36	51	44	46	38	37	NR
2·0	3·8	3 8	4 2	4 4	4 5	4 4	4 8	4 0	4·6 to 5·3
42	NR	NR	NR	NR	51	NR	NR	NR	NR
5·3	6·4	NR	NR	NR	6·2	NR	NR	NR	5·2 to 6 4
27	84	24	21	9	11	11	11	16	19*
<50	80	98	95	98	94	97	98	98	96
Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	None
9 1	11 3	17 8	0	35 2	4 5	2 0	2 5	4 4	0 to 0 75
0 43	NR	NR	NR	NR	NR	NR	NR	NR	NR

increased ventilatory excursions, she did not achieve the same degree of hypocapnia as the other patients. She had bronchospasm during the recording, having suffered bronchial asthma for the previous two years.

Periods of hyperventilation were often interrupted by pauses in inspiratory efforts, some of them prolonged (≥20 seconds) (table 2, fig 2, and fig 3). These prolonged pauses were not induced by seizure activity as shown by surface electroencephalography recordings (fig 3) except on one occasion (case 9). Most of these pauses contained a Valsalva manoeuvre[12] during which the large inspiratory airflow associated with hyperventilation was followed at the end of inspiration by active expiratory muscle activity but no expiratory flow.

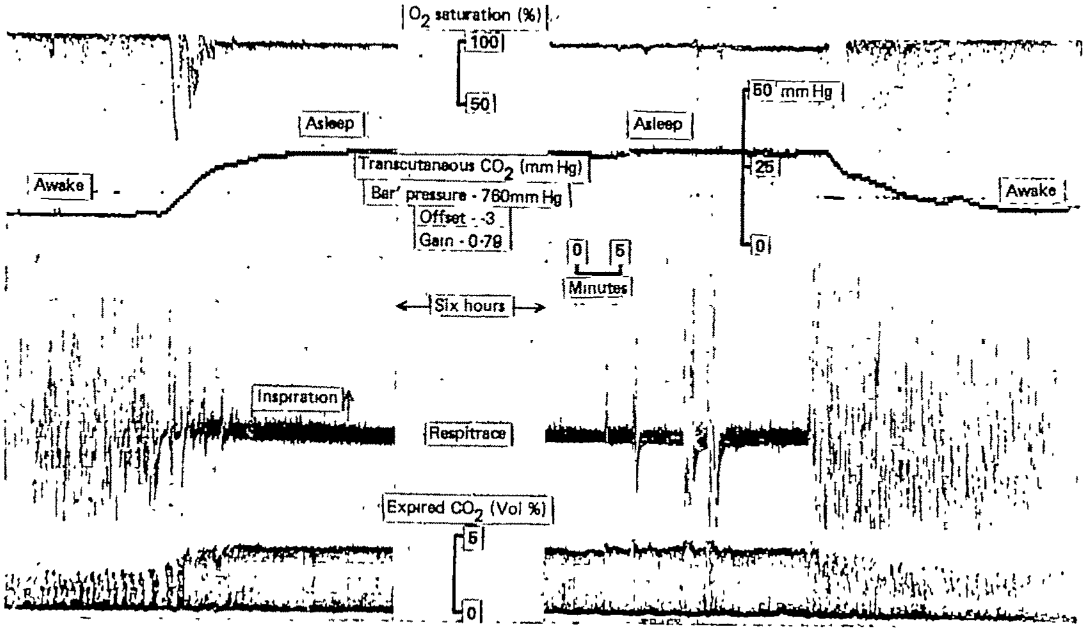

Fig 1 *Interrupted printout of an overnight tape recording (case 5) showing transition from awake to asleep and back again. During the awake periods before and after sleep there is hyperventilation with a transcutaneous carbon dioxide down to 8 mm Hg. During sleep the transcutaneous carbon dioxide and end tidal carbon dioxide are normal.*

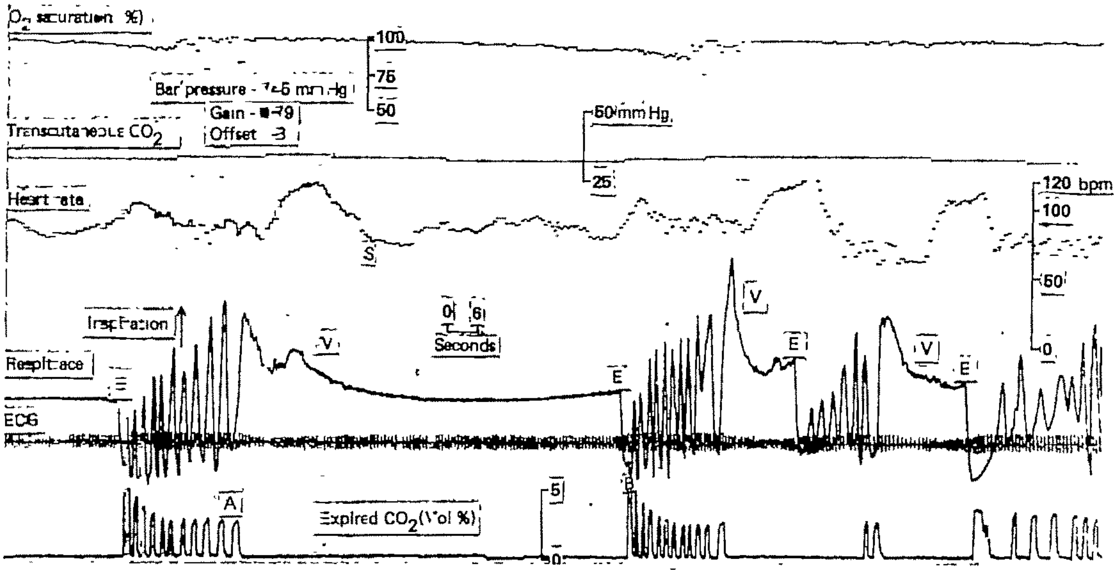

Fig 2 *Section of recording when awake (case 2). Four episodes of apnoea each associated with Valsalva manoeuvre (V) are shown, the longest reading 77 seconds (from A to B) during which there is a small fall in oxygen saturation (to 90%) Preceding each pause the end tidal carbon dioxide is reduced by a period of hyperventilation to about 2·4 volume %. After the prolonged pause (AB) the end tidal carbon dioxide reaches 5·0 volume %. Throughout recording the transcutaneous carbon dioxide is about 32 mm Hg. Each apnoeic episode begins at end of inspiration. Lung volume is maintained (by Valsalva manoeuvres) until positions E where there is sudden expiration of gas and the immediate onset of hyperventilation During periods of hyperventilation and the early part of the apnoeic pause (Valsalva manoeuvre) there is a comparative bradycardia. Increase in heart rate begins within six seconds of onset of the pause About 26 seconds (position S) into the prolonged apnoeic episode (AB) the heart rate slows again.*

After a variable period of time, during which portions of the gas within the lungs were often expired with a 'cry like' sound through a partially closed glottis, there was sudden expiratory release of the remaining gas (fig 2) This was followed by another inspiratory effort with inspiratory airflow and the beginning of a new bout of hyperventilation. During periods of normal ventilation, particularly when asleep, such 'apnoea/Valsalva' manouevres were not seen.

During prolonged apnoeic periods, oxygen saturation often dropped (table 2, fig 2, and fig 3) though there was usually a considerable delay before the level fell below 90%. Sometimes this hypoxaemia was associated with central cyanosis and a transient lack of awareness. None of the children were hypoxaemic at the onset of a change from normal breathing to hyperventilation (fig 4). The prolonged apnoeic pauses were a consequence of the hyperventilation not the reverse.

All 10 patients with hyperventilation had apnoeic pauses of ≥20 seconds (table 2). Their median duration was 35 seconds and the longest was 125 seconds. The number of these prolonged pauses varied from 0·12 to 11·54 p/hour of recording, median 1·96/hour.

The time between the onset of the apnoeic pause and the dip in oxygen saturation to < 90% varied from 8 to 124 seconds (median 33). Of prolonged pauses, 47% were accompanied by dips in oxygen saturation below 90%. In five patients oxygen saturation fell below 50% during some of the prolonged apnoeic pauses.

During sleep case 2 had raised transcutaneous end tidal carbon dioxide, abnormal episodes of arterial hypoxaemia (to <80%) accompanied by partial or complete absences of airflow, and an abnormal inspiratory waveform pattern typical of upper airway obstruction,[13] that is an initially rapid inspiratory movement followed by a slower movement reflecting the increased inspiratory resistance. Case 9 had a recent history of seizures associated with central cyanosis and loss of consciousness. One of these seizures was recorded. The sequence identified was as follows: after waking from sleep the transcutaneous carbon dioxide fell progressively with hyperventilation from 50 mm Hg to about 26 mm Hg. One particular episode of hyperventilation was associated with the development of seizure discharge on the electroencephalogram. The onset of this seizure coincided with pallor, dilation of

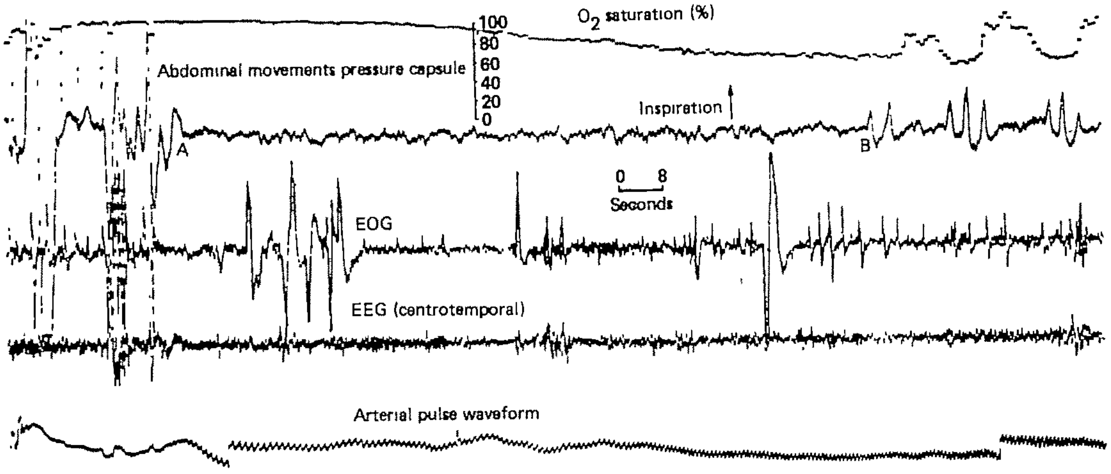

Fig 3 *Prolonged apnoeic pause (A–B) of 125 seconds (case 4). The electro-oculogram and electroencephalogram recordings show that the child was awake and there was no evidence of an associated seizure.*

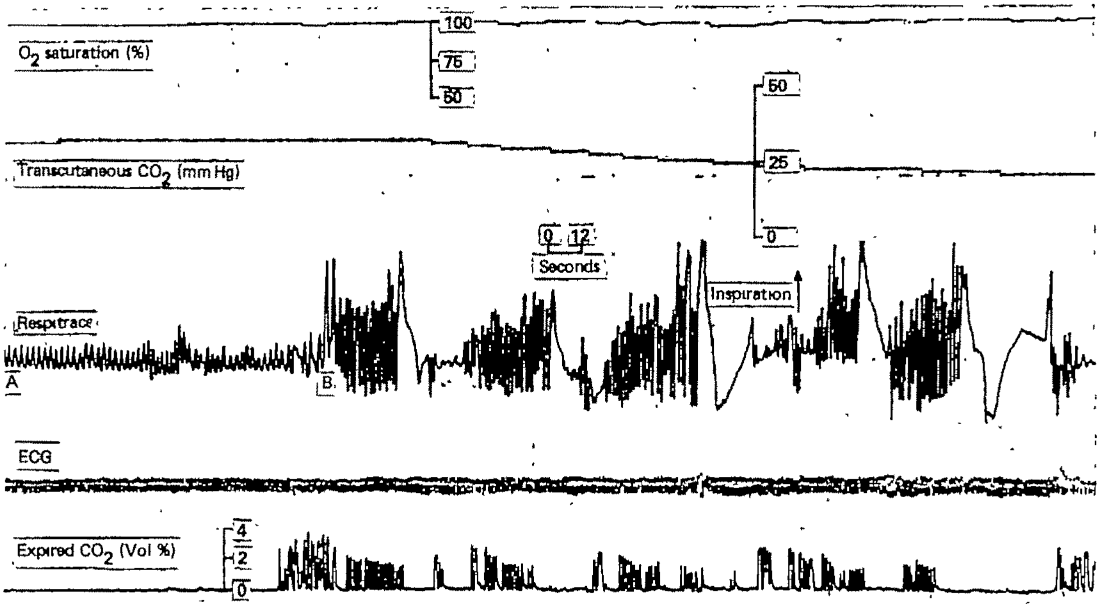

Fig 4 *Section of daytime recording (case 5). An episode of breathing without hyperventilation (A to B) is followed by periods of hyperventilation (as shown by end tidal carbon dioxide and the increased amplitude and frequency of the breathing movements) and apnoeic pauses. Hyperventilation episodes are accompanied by a progressive fall in trancutaneous carbon dioxide. There is no evidence of hypoxaemia preceding the onset of hyperventilation (oxygen saturation 98–100%)*

pupils, and a blank facial expression. The child sat erect, then fell back with grey twitching lips and appeared to lose consciousness. Clutching movements of the hands and jerking of the trunk preceded recovery. At the time of onset of the seizure there was prolonged inhibition of inspiratory efforts (without a Valsalva manoeuvre) for the duration of the seizure (about 59 seconds). Hypoxaemia developed during this prolonged apnoea and became severe (oxygen saturation <50%). As the seizure discharge on the electroencephalogram became less intense, a large inspiratory effort occurred producing gradual recovery from the hypoxaemia.[14]

In cases 1, 4, and 7, QT intervals (corrected for heart rate using Bazett's formula) were at the upper limit of normal during periods of hyperventilation (table 2) (normal range mean (SD) 0·404 (0·026) seconds[15]).

All seven patients who had blood samples taken during hyperventilation (table 3) showed respiratory alkalaemia, plasma chloride concentrations at the upper limit of normal, and reduced plasma bicarbonate concentrations. Ionised calcium concentrations were in the lower normal range and plasma lactate concentrations were in the upper normal range.

GROUP 2 (CASES 11–14)

There were four patients in group 2 with an average age of 15·0 years; they were older than those in group 1 (table 1). All four gave histories suggestive of hyperventilation in earlier childhood, and in case 11 respiratory alkalaemia had been documented at the age of 5. Though there was no evidence of hyperventilation during recordings when awake, each patient had frequent apnoeic pauses with Valsalva manoeuvres. In three, the apnoeic pauses exceeded 19 seconds. These pauses occurred particularly when the child became excited or frightened and were sometimes accompanied by pronounced changes in heart rate. During sleep, apnoea/Valsalva events were not detected and the breathing patterns seemed normal.

GROUP 3 (CASES 15–18)

There were four patients in group 3 with an average age of 8·3 years. Three of these patients had no previous history of hyperventilation, and in one the description was unconvincing. All but case 17 had apnoea/Valsalva events when awake but these episodes were much less frequent than those present in patterns in group 2. None had apnoeic pauses exceeding 15 seconds.

Two further breathing patterns were identified: firstly, episodes of periodic apnoea were seen in 15 of the 23 (65%) controls (durations 0·05 to 0·75 minutes/hour of recording: median duration of those with periodic apnoea 0·13 minutes/hour). Only one of the 18 patients with Rett syndrome (case 13) had no periodic apnoea. All the remaining patients had larger quantities than the controls (1·7 to 56·1 minutes/hour: median 11·3 minutes/hour). Cases 1–10 with hyperventilation had values for periodic apnoea varying from 1·7 to 56·1 (median 12·4) minutes/hour. Cases 11–14 who had past histories of hyperventilation, had values for periodic apnoea varying from 0 to 35·2 (median 14·5) minutes/hour. The values of periodic apnoea for cases 15–18 varied from 2·0 to 4·5 (median 3·4 minutes/hour).

The second pattern was exemplified by case 10 who had brief episodes of hypoxaemia during which breathing movements and airflow continued. None of these episodes included the abnormal inspiratory waveforms typical of upper airway obstruction documented in case 2; this pattern of breathing and hypoxaemia was not found in the controls.

Discussion

Abnormal hyperventilation, with consequent hypocapnic alkalaemia present only during active wakefulness, was the major respiratory abnormality that we found in this group of children with Rett syndrome. We found hyperventilation in 56% of patients, and in an additional 22% (generally older children) there was a history suggesting it. We do not have an adequate explanation for the hyperventilation of Rett syndrome. Because it does not occur during sleep we speculate that it is likely to result from excessive stimulation of the respiratory control centres in the brain stem or from abnormally reduced higher centre inhibition.[16–18] Hypoxaemia did not precede the change from normal breathing to hyperventilation and therefore cannot be the primary cause of the hyperventilation.

Three other patterns of breathing were identified in our patients. The first and most common was a prolonged absence of inspiratory efforts (≥20 seconds), and was first described by Lugaresi *et al.*[4] In our patients prolonged apnoeic pauses invariably occurred immediately after an episode of hyperventilation and therefore only when they were awake. In the four patients who did not have hyperventilation but did have history of it (group 2), prolonged pauses also occurred only when they were awake. The onset of hypoxaemia occurring during prolonged apnoeic pauses was comparatively delayed, possibly because large stores of oxygen were present in the lungs as a result of the hyperventilation. Most of the prolonged apnoeic pauses included a Valsalva manoeuvre.[12] The stimulus to breathe in and terminate the prolonged apnoea was probably associated with an increase in carbon dioxide, and sometimes with hypoxaemia. Hyperventilation in healthy human adult subjects does not result in a prolonged absence of inspiratory efforts; this response has been described only when there was diffuse disease of the forebrain,[16] or when the subject was anaesthetised or heavily sedated.[17] In case 9 a clinical seizure occurred during hyperventilation and was associated with a prolonged absence of inspiratory efforts.

The second pattern, periodic apnoea,[11] occurred in both patients and controls. In all but one of the patients with Rett syndrome, values exceeded those in the control group (table 2) by ratios of 2:1 to 75:1. Increases were particularly noticeable in patients with hyperventilation or with a history of hyperventilation. Some of these increases in periodic apnoea undoubtedly reflected the apnoea/Valsalva manoeuvres that frequently occurred in succession. Sometimes the intervening episodes of apnoea were associated with hypoxaemia. Cheyne-Stokes breathing (a form of periodic apnoea) has previously been described in association with hyperventilation by Brown and Plum.[19]

The third pattern, that of continued inspiratory efforts and inspiratory airflow but with accompanying hypoxaemia, was found in one patient (case 10). There was no evidence of partial upper airway obstruction, and these findings could suggest the presence of a mismatch in ventilation/perfusion associations (possibly through areas of alveolar atelectasis).[20] It is possible that in this patient hyperventilation had impaired the function of lung surfactant.[21]

Our findings that respiratory abnormalities in patients with Rett syndrome are present only when they are awake confirm those of Glaze *et al*[5]; we do not, however, agree with these authors that the hyperventilation is compensating for periods of disorganised breathing and hypoxaemia. Our recordings clearly show that hyperventilation is the primary problem and that its onset does not occur in response to hypoxaemia, rather, hypoxaemia is a consequence of the prolonged apnoeic episodes induced by the hyperventilation. Unlike Glaze *et al*[5] we found that breath holding and Valsalva manoeuvres occurred often in 14 of our 18 patients. Their finding that end tidal carbon dioxide was normal during disorganised breathing does not concur with our results. The lack of a plateau on the expired carbon dioxide trace shown in their figure could be one reason for their failure to identify the low end tidal carbon dioxide values indicative of hyperventilation.

There are interesting parallels between some of the characteristic features of Rett syndrome that we have described and the hyperventilation syndrome that is documented in children and adults in which the following signs have been reported: peripheral vasoconstriction,[22-24] neuromuscular irritability leading to tetany and muscle contractures,[25] parasthesiae and a lowered pain threshold[26]; and the induction of seizures.[27]

There are also biochemical parallels between the hyperventilation syndrome and Rett syndrome. Respiratory alkalaemia (a consequence of hyperventilation) produces a compensatory reduction in plasma bicarbonate ions.[23-24] This is accomplished by an increase in renal excretion and a corresponding retention of ammonium ions, and by influx of bicarbonate ions into the cells in exchange for chloride ions. These compensatory mechanisms may result in a decrease in plasma bicarbonate and an increase in plasma chloride and ammonia concentrations. Alkalaemia may also increase the concentrations of lactate and pyruvate in plasma and cerebrospinal fluid.[28] These biochemical findings, sometimes unconfirmed, have been reported in Rett syndrome.[1 29 30] Increased plasma chloride concentrations, decreased plasma bicarbonate concentrations, and lactate concentrations at the upper limit of normal were identified during hyperventilation in our patients (table 3).

Hyperventilation produces not only vasoconstriction in the skin but, of more importance, in the cerebral circulation.[27] Moreover, alkalaemia induces a leftward shift in the oxygen dissociation curve, and theoretically may impair the unloading of oxygen to the cerebral tissues. In combination with the extracellular alkalaemia,[28] these effects may also increase cerebral lactic acid concentrations. The abrupt and extreme changes in cerebral blood flow that accompany sudden changes in carbon dioxide concentrations between being awake and being asleep may adversely affect cerebral perfusion. Together with the hypoxaemia accompanying abnormal apnoeic episodes, these mechanisms may contribute to the development of the cerebral impairment that has been reported in Rett syndrome.[31 32] Further studies of changes in cerebral blood flow in children with Rett syndrome and hyperventilation are indicated.

Sudden unexpected death has been reported in Rett syndrome.[33] Two of the 19 children referred to in our original papers of 1985 and 1986[2 3] have since died suddenly and unexpectedly aged 11 and 16 years. The known effects of disturbances of pH and ionised calcium on cardiac muscle excitability,[22-24] and the propensity of hypocapnia to reduce coronary artery perfusion[34] may be important in some cases.[35] One further danger was seen in case 9 in which hyperventilation seems to have led to inhibition of inspiratory drive induced by seizure and resulting in prolonged and severe hypoxaemia.

Because severe and persistent hyperventilation could contribute to deterioration of central and peripheral neurological function in Rett syndrome it seems wise to detect and treat this component of the syndrome early in life. Monitoring of end tidal/transcutaneous carbon dioxide can be done by non-invasive and comparatively straightforward techniques that could be applied to infants or young children presenting with developmental delay of unknown cause. Clinical observations alone are unreliable in the diagnosis of hyperventilation; this difficulty has been well described in adults with the hyperventilation syndrome where only occasional breaths of large tidal volume may be needed to maintain severe hypocapnia.[35]

In conclusion, hyperventilation is an important feature of Rett syndrome and its respiratory, neurophysiological, biochemical, and vascular consequences may contribute to the characteristic features of the syndrome. Further studies are required to determine whether correcting the hyperventilation will benefit patients with Rett syndrome. Hyperventilation appears to be the cause rather than the result of hypoxaemia.

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Juvenile myoclonic epilepsy

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SUMMARY The clinical and electroencephalographic features of 10 adolescents with juvenile myoclonic epilepsy are presented. The mean age on onset was 12·3 years. Myoclonic jerks, predominantly on awakening, occurred in all 10 and were associated with infrequent generalised tonic-clonic seizures in nine. Five had first degree relatives with seizures. The neurodevelopmental status was normal in eight and social integration good in seven. Waking interictal electroencephalograms showed normal background activity in nine, polyspike and wave in six, and single spike and wave in eight. Four were photosensitive. Failure to respond to other antiepileptic drugs was usual, but valproate monotherapy resulted in good or complete seizure control. Juvenile myoclonic epilepsy is a well defined clinical entity that responds well to valproate and is usually associated with a good outlook.

Of the childhood epilepsies, those which include myoclonic jerks cause most confusion, and especially in younger children are most likely to be drug resistant. Juvenile myoclonic epilepsy appears to be a distinct and relatively benign epileptic syndrome. Although well recognised in literature from continental Europe and the United States juvenile myoclonic epilepsy has apparently not been studied in detail in Britain.[1–7] We aim to draw attention to this epileptic syndrome. Our findings in 10 patients with seizures typical of juvenile myoclonic epilepsy are presented. The clinical and electroencephalographic features, and responses to antiepileptic drugs, are reviewed.

Patients and methods

Between 1981 and 1987, 10 adolescents (five boys and five girls) with recent onset of myoclonic jerks, and in most cases associated generalised tonic-clonic seizures, attended the paediatric neurology clinic, University Hospital of Wales. Five were referred by general practitioners and five by consultant paediatricians. On presentation a full history of seizures was taken for both the patients and their first degree relatives. Information was collected on the perinatal and medical histories, as well as developmental, social, and educational details. General physical and full neurological examinations were performed on each patient and all had 'routine' 15 to 20 minute electroencephalographic recordings with hyperventilation and photic stimulation. The response to previous anticonvulsant treatment and to the introduction of valproate monotherapy was assessed.

Results

SEIZURE TYPES AND CHARACTERISTICS

The seizure types at onset and the intervals between myoclonic jerking and generalised tonic-clonic seizures are shown in table 1, with the ages at onset. In eight patients the myoclonic seizures occurred almost exclusively on awakening in the morning. Similarly, six of the nine patients with generalised tonic-clonic seizures had their seizures predominantly in the early morning after a series of myoclonic jerks. Three of the four girls who had reached menarche described an increase in myoclonic jerking at menstruation. Two patients noticed that their jerks were induced by a television or computer screen.

PREVIOUS SEIZURES AND FAMILY HISTORY OF SEIZURES

Two boys had a history of febrile seizures. One girl had a history of unexplained 'fainting attacks' from 7 years of age. Five patients had a first degree relative with a history of seizures. In three cases there was a history of febrile seizures in siblings, one patient had a sibling with absence seizures, and in another the father had a history of infrequent, early morning generalised tonic-clonic seizures.

PERINATAL AND MEDICAL HISTORY

The perinatal course was uneventful in all but one boy, who had been born by emergency caesarean

Table 1 *Seizure types and characteristics*

Patient No	*Sex*	*Seizure type at onset*	*Age at onset*	*Age at first GTCS*	*Interval between onset myoclonus and first GTCS (months)*
			(decimal years)		
1	M	GTCS+myoclonus	9·5	9·5	0
2	M	Myoclonus	10·8	11·7	10
3	M	Myoclonus	10·9	(GTCS did not develop)	
4	F	GTCS+myoclonus	11·6	11·6	0
5	F	GTCS+myoclonus	12·1	12·1	0
6	M	Myoclonus	12·7	12·9	3
7	F	Myoclonus	12·8	12·9	1
8	F	Myoclonus	13·5	14·1	7
9	M	Myoclonus	13·8	14·1	4
10	F	Myoclonus	15·7	15·8	1

GTCS=generalized tonic-clonic seizure
Mean age at onset of seizures 12·3; mean age at first GTCS, 12·7
Mean interval from myoclonus to GTCS in those presenting with myoclonus alone was 4·3 months

section at term; he had done well after 24 hours observation on a special care baby unit. The medical history was unremarkable in nine; one patient had a posterior fossa medulloblastoma removed at 2 years of age. He had had surgery followed by courses of radiotherapy and chemotherapy, which were completed six years before the onset of seizures.

DEVELOPMENTAL HISTORY

Although not seriously delayed, three patients had first walked after 17 months of age and one of these had also had mildly delayed speech. The developmental history was unobtainable in one girl; she may also have had some delay as, at presentation, she was receiving schooling for the educationally subnormal (moderate).

SCHOOLING, BEHAVIOUR, AND SOCIAL INTEGRATION

Nine patients attended normal school, of whom two required remedial teaching. One received schooling for the educationally subnormal (moderate). Overt behavioural disturbance was reported in two patients who had outbursts of uncontrollable rage. Social integration was appropriate for age in all but three patients. Two lacked confidence and were unreliable with tasks such as shopping. One girl was described as 'rude and rebellious' and did not mix well with her peers.

NEUROLOGICAL EXAMINATION

Neurological examination was normal in seven patients. Of the other three, one was mildly dyspraxic, a second had a minimal hemiparesis. Only the patient with a previous medulloblastoma had more than a minimal disability; he had pronounced dyspraxia.

GENERAL EXAMINATION

General examination was normal in all but one girl who was very short in stature due to unknown causes despite prior investigation.

RESULTS OF ELECTROENCEPHALOGRAPHY (TABLE 2)

The background rhythms were normal in nine patients. The records of six patients showed a generalised and symmetrical polyspike and wave pattern. Of the records of the remaining four, one showed spike and wave activity on hyperventilation, one showed bursts of generalised slow waves and sharp waves accentuated by hyperventilation, and one showed sharp waves and an isolated 'near spike' in the right temporal leads on hyperventilation. In the patient who had had a previous medulloblastoma, spike and wave with pronounced slow wave abnormalities, variable asymmetries, and bilateral phase reversals were recorded. Four patients displayed appreciable photosensitivity and of these, two had a myoclonic photoconvulsive response.

RESPONSE TO TREATMENT

Before attendance at the clinic six patients had been prescribed phenytoin, carbamazepine, or clonazepam, singly or in combination. One showed a partial response to phenytoin, but the dose required produced toxicity. Another showed an unsatisfactory partial response to combination treatment with carbamazepine and clonazepam. The remaining four showed no response to previous treatment. On the other hand, sodium valproate was effective and well tolerated in all our patients. Seven showed cessation of all seizures and in the remaining three cases there was an appreciable reduction in seizure frequency.

Table 2 *Results of electroencephalography (All recordings were made with the patient awake and interictal)*

Patient No	*Background activity*	*Isolated spikes*	*Polyspikes or polyspike/wave*	*Spike and wave*	*Abnormal bursts of slow waves*	*Sharp waves*	*Photosensitivity*
1	Normal	+	+	+	+		*
2	Abnormal			+	+		
3	Normal	+	+	+			†
4	Normal			+			
5	Normal	+	+	+			†
6	Normal		+	+	+		
7	Normal	+				+	
8	Normal	+	+	+	+	+	
9	Normal				+	+	
10	Normal		+	+			*

+=Present
*Appreciably photosensitive, †very photosensitive with photoconvulsive jerks

Discussion

The International Classification of Seizures into partial and generalised forms is well known.[8] The characterisation of 'epileptic syndromes' by seizure type(s), together with specific findings on electroencephalography and particular neurological or intellectual abnormality,[9] however, has been less widely practised. The recognition of an epileptic syndrome can help in determining the treatment most likely to control seizures, possible associated problems and the prognosis. Better known examples of such epileptic syndromes include West syndrome, Lennox-Gastaut syndrome, and 'benign partial epilepsy with centro-temporal (Rolandic) spikes'.

At a prevalence of between 4% and 5·4%,[2 10 11] juvenile myoclonic epilepsy is almost as common as classical absence epilepsy (petit mal), which occurs in about 6% of epileptics.[12] Despite this it remains an underappreciated syndrome, usually unrecognised by the referring clinicians [2]

Onset around puberty is a very characteristic feature.[2 3 5 7 9-11 13 14] At least three quarters of all cases start in the second decade.[7 10 11] The mean age of onset of myoclonias in the present series was somewhat younger than those from other reports,[2 3 7 10 11] but the latter have included young adults in contrast with our purely paediatric case load.

In juvenile myoclonic epilepsy the seizures are virtually always of two types and occur almost exclusively on morning awakening.[3 5 7 10 11 15] Bilateral single or repeated, arrhythmic, irregular myoclonic jerks without loss of conciousness are noted predominantly in the arms, and infrequent generalised tonic-clonic seizures, which may occur separately or more commonly follow a series of myoclonic jerks, can also be present.[2 5 7 9-11 13 15] Sleep deprivation,[3 7 10 15 16] excessive alcohol intake,[3 7 10 16] emotional stress,[7] and menstruation[7 10 11 13] may precipitate the seizures. Nine of our 10 cases had generalised tonic-clonic seizures as well as myoclonic jerks; a proportion comparable with that in other series.[3 7 10 11] In most cases the myoclonic jerks are present for some time (months or years) before generalised tonic-clonic seizures occur and may then be erroneously considered to be hysterical.[2 10] Reflecting the somewhat younger age in our cases, the onset of generalised tonic-clonic seizures followed relatively soon after the myoclonias. Four of our 10 patients had clinical or electroencephalographic responses to photic stimulation, in keeping with the observation that virtually no other epileptic syndrome is as closely related to photosensitivity as juvenile myoclonic epilepsy.[14]

Genetic factors are clearly of aetiological importance. Half of our cases had first degree relatives with seizure disorders. In other series between 25% and 50% of patients have a family history of seizures.[3 7 10 11] Only one of our patients had more than minimal abnormalities on neurological examination and these were probably attributable to previous intracranial surgery, radiotherapy, and chemotherapy. The almost invariable normality of patients in other series has been emphasised.[2 3 7 10 11 15] Almost all patients are reported to be of average intellect,[2 3 5 6 10 15] and all but one of the children in our series were being educated in normal schools. There may, however, be a tendency to an immature personality trait and social maladjustment.[6 7 10 15]

When abnormal, the electroencephalogram can provide very helpful confirmatory information. Interictally the background activity is nearly always normal,[2 3 5 10 13] and epileptic discharges are characterised by multitudes of spikes occurring bilaterally, bilaterally synchronous spike and wave, and the particularly characteristic polyspike-wave complexes. Repetitive spike and wave complexes always occur at a frequency greater than 3 and usually at 3·5 to 4 5 cycles/second.[2,3,5,7,10,13] Abnormalities are more likely to be found on records obtained early in the day,[10] after sleep deprivation,[2,3,10] or after plentiful intake of alcohol or coffee.[10] Hyperventilation is not very provocative, but intermittent photic stimulation commonly produces polyspike-wave discharges [2,3,10,14]

The lack of neurological and intellectual deterioration in juvenile myoclonic epilepsy, together with a normal background electroencephalogram, help to distinguish it from the 'progressive myoclonic epilepsies' such as Baltic myoclonus epilepsy, Ramsay Hunt syndrome, myoclonic epilepsy with ragged red fibres, etc, in which progression to dementia and paralysis is almost invariable.[17] Juvenile myoclonic epilepsy must also be differentiated from the rarer 'epilepsy with myoclonic absences' in which generalised, rhythmical, regular myoclonic jerking occurs during a period of altered conciousness and the electroencephalogram shows 3/second spike and wave.[18]

Absence seizures have been reported in association with juvenile myoclonic epilepsy but were not present in any of our patients.[2,3,5,7,15,19] In some of these reports adolescents with absences as well as myoclonic jerks and generalised tonic-clonic seizures appear to have more severe seizure disorders,[2] and it has been suggested that, rarely, transitional forms of myoclonic absences and juvenile myoclonic epilepsy may occur.[15] On the basis of the very good outlook for those who have early morning myoclonias and generalised tonic-clonic seizures only, we suggest that patients with absences in addition should not be classified as having juvenile myoclonic epilepsy.

In the prevention of seizures in juvenile myoclonic epilepsy, it is clearly important to avoid sleep deprivation and excessive intake of alcohol or coffee. In addition, it is usually necessary to use antiepileptic treatment. In common with the findings of all other reports,[2,3,13,15,20–22] the present series shows the very specific efficacy of valproate. Our patients are still too young for the long term outcome to be considered In studies with long follow up periods, good control of seizures is maintained with continued valproate, but even after many years, recurrence of the seizures is almost invariable if valproate is withdrawn (J Roger, personal communication).[7,15]

In conclusion, juvenile myoclonic epilepsy is a well defined epileptic syndrome in which myoclonic jerks and infrequent generalised tonic-clonic seizures occurring on morning awakening start at puberty A close family history of primary generalised seizures is common and the neurological and intellectual status is usually normal The electroencephalogram may be normal but more usually, particularly if recorded early in the morning, shows multitudes of spikes, spike and wave, and polyspike-wave complexes, frequently with photosensitivity. The seizures respond well to valproate, but are resistant to other antiepileptic medication The outlook for freedom from seizures is very good provided valproate is continued, but relapse is usual if treatment ceases.

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Urinary mannitol:lactulose excretion ratios and jejunal mucosal structure

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SUMMARY A dual sugar (mannitol, lactulose) absorption test was evaluated using an iso-osmolar oral dose in two groups of children: a study group of 43 children divided into five subgroups, based on severity of mucosal damage, and a control group of 53 children with histologically normal jejunal biopsy specimens. After an oral dose, the three hour urinary mannitol:lactulose ratios in the control group showed a highly significant positive correlation with body surface area. After correction for the body surface area relationship, a control lower limit was defined by the mean −2SD of the $\log_{10}$ transformed control mannitol:lactulose ratios.

Specificity and sensitivity for severe villous atrophy was 98% and 95% respectively but the sensitivity declined rapidly with decreasing degrees of mucosal damage, and the test would not therefore be an adequate screening procedure for all enteropathies. In sequential studies in 18 children, the changes in the mannitol:lactulose ratio were consistent with the changes in mucosal structure induced by gluten challenge or gluten withdrawal. The test may therefore have a role in any sequential study of lesions of the mucosa of the small intestine.

The diagnosis of a small intestinal enteropathy can be made only by jejunal biopsy. Non-invasive tests, such as the xylose absorption test have been used as preliminary screening procedures[1] but they have limitations.[2] Although satisfactory in principle, the inherent variables of gastric emptying, intestinal transit and blood flow, and renal function reduce the correlation between xylose absorption or excretion and the degree of mucosal damage.[2] The search for improved screening tests has continued and most recently a dual sugar absorption test has been proposed.[3 4] Dual sugar absorption tests are non-invasive and have the additional advantage of eliminating many of the variables associated with the single sugar absorption tests. Dual sugar absorption tests have been shown to be effective as screening tests for coeliac disease in adults.[5–7] The test has been used in a number of studies in children,[8–12] but its role as a diagnostic procedure for mucosal damage in childhood has not been fully validated.[13 14]

We have therefore assessed the value of a dual sugar test (mannitol-lactulose), by determining its efficiency in three potential applications: as a screen for an enteropathy; for assessing dietary compliance during gluten withdrawal; and for determining an appropriate time for a post gluten challenge biopsy.

Patients and methods

SCREENING STUDY

The study group comprised 43 children undergoing jejunal biopsy for investigation of gastrointestinal symptoms (median age 6·8 years, range 0·4–17·2 years). All had either villous atrophy, of varying severity, or histological abnormalities without villous atrophy. They were divided into five groups by severity of histological abnormality, in a single blind situation, by the histopathologist of the Children's Hospital, Birmingham, using the criteria of Whitehead.[15] The five groups comprised: subtotal villous atrophy (n=14); severe partial villous atrophy (n=3); partial villous atrophy (n=6); mild, patchy partial villous atrophy (n=8); and increased cellularity of the lamina propria but no villous atrophy (n=12).

The control group comprised a further 53 children (median age 4·6 years, range 0·8–17·9 years) with gastrointestinal symptoms but whose jejunal biopsy specimen was histologically normal. None had a history of atopy.

DIETARY COMPLIANCE STUDY

In this part of the study nine children from the screening investigation, who had subtotal villous atrophy, started a gluten free diet. In addition, eight children who were maintaining a histologically normal jejunal mucosa, while on a gluten free diet, started gluten challenge (20 g gluten/day). Dietary compliance was assessed at intervals of four to six weeks by the dietetic department of the Children's Hospital, Birmingham. The dietary findings were not communicated to the clinical investigators until the end of the study.

JEJUNAL BIOPSY

All patients in the study had one or more peroral jejunal biopsies as part of their routine gastrointestinal investigations Biopsy specimens were obtained just distal to the ligament of Treitz using a paediatric size Watson modification of the Crosby capsule, positioned with fluoroscopy. None of the patients had bacterial contamination of the small bowel at the time of biopsy.

DUAL SUGAR (MANNITOL-LACTULOSE) ABSORPTION TEST

After an overnight fast (six to eight hours in infants) and after passing the first morning urine specimen (the 'fasting specimen'), the test sugar solution was ingested. After one hour, the test subjects were encouraged to drink water freely to increase urine flow but no other drinks or food were permitted for a further two hours when the test ended. The fasting specimen and all urine specimens passed during the test period (the 'test specimens') were saved separately in bottles containing 0·5 ml 10% w/v sodium azide. The time of each test specimen was recorded.

The test sugar solution contained 10 g/l mannitol and 75 g/l lactulose (274 mosm/l) and 0·1% Nipasept preservative. The dose was body surface area related (100 ml/square metre) with lower and upper dose limits of 20 and 100 ml.

The test was done within two days of the jejunal biopsy in 85% of the children and within five days in the remaining 15%. In the 17 children on gluten withdrawal or challenge, the tests were carried out at intervals of four to six weeks using the same sugar dose throughout for a given patient. None of the children was receiving drugs before or during the investigations. The test procedure was approved by the local ethical committee and informed verbal consent was obtained from parents of all the children before testing.

MANNITOL AND LACTULOSE ASSAY

All urine samples were stored at −20°C until analysed. All test urines passed up to three hours after the sugar dose were pooled before analysis. Pooled samples were prepared for analysis by centrifuging cold to remove any deposit followed by desalting with Amberlite MB-1, acetate form. The volume of desalted urine containing 2 μmol creatinine was further purified by preparative thin layer chromatography on foil-backed plates.[16] Areas of the plates corresponding to mannitol and lactulose standards were excised and eluted with acetonitrile:water (72·5:27·5 v/v) and the eluant dried under vacuum. The residue was dissolved in 200 μl acetonitrile:water just before chromatographic analysis. Mannitol and lactulose were measured by high performance liquid chromatography using a 250×5 mm Spherisorb-5 amino column (Phase Separations Ltd) or 250×4 mm LiChrosorb amino column (E Merck) eluted with acetonitrile:water (72·5:27·5 v/v) at 1·5 ml/minute. Eluted solutes were detected with a mass detector (Applied Chromatography Systems) and quantitated by comparison with standard mannitol-lactulose mixtures, peak areas being measured by a Milton-Roy Cl–10 integrator. Test results were expressed as the mannitol:lactulose concentration ratio measured in the three hour post sugar ingestion urine pool.

Tests with fasting urines containing more than a trace of solutes with chromatographic retention times corresponding to mannitol or lactulose were discarded. All analyses were done in duplicate from the desalt stage and mean values taken. The coefficient of variation of differences between duplicate analyses was 2·5%. The recovery of mannitol and lactulose added to sugar free urine was 85% or greater.

The statistical analysis was non-parametric. Spearman's rank correlation coefficient was used to determine the degree and significance of association of two variables.

(Mannitol is a hexitol not a hexose but has been designated 'sugar' in this report for convenience).

Results

SCREENING STUDY

Despite the use of a body surface area related sugar dose, mannitol:lactulose ratios showed a significant positive correlation with body surface area in the control children ($r=0{\cdot}646$, $p<0{\cdot}001$). The relationship was similar in children with villous atrophy but was less pronounced (fig 1). The ratios were therefore corrected for body surface area (ratio/BSA). The corrected data from the control group exhibited a positive skew and it was therefore $\log_{10}$ transformed before determining population parameters. The lower limit of the control distribution shown in fig 2 is the mean −2SD of the $\log_{10}$ transformed control data (mannitol:lactulose ratio of 3·09).

Fig 2 shows the corrected mannitol:lactulose ratios for the study and control groups. All but one

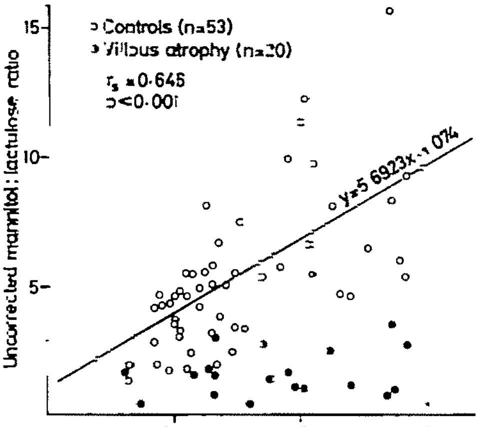

Fig 1 *Three hour urinary mannitol:lactulose ratio–body surface area relationship. Children with villous atrophy comprised 14 with subtotal villous atrophy, three with severe partial villous atrophy, and three with partial villous atrophy. The body surface area correlation data applies only to the control group.*

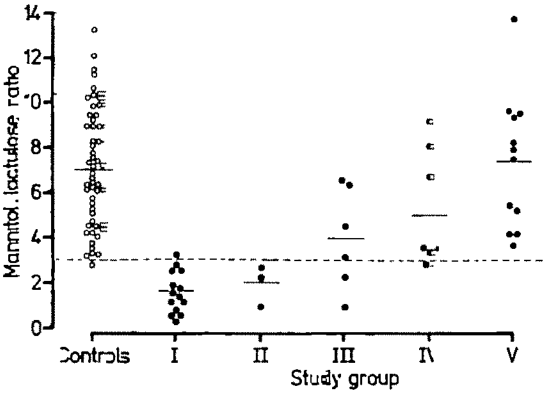

Fig 2 *Body surface area corrected mannitol lactulose ratios in control and study groups. The study group was divided into five subgroups based on severity of mucosal damage. I=subtotal villous atrophy (n=14); II=severe partial villous atrophy (n=3); III=partial villous atrophy (n=6); IV=mild, patchy partial villous atrophy (n=8); and V=increased cellularity of the lamina propria without villous atrophy (n=12). The horizontal bars show the mean value for each subgroup. The broken line denotes the lower limit of the control range defined by the mean −2SD of the* log_{10} *transformed control mannitol:lactulose ratios.*

of the 17 children with severe mucosal damage (subtotal villous atrophy or severe partial villous atrophy) had ratios below the lower limit of the control range. Lesser degrees of villous atrophy or histological abnormality were associated with ratios within the control range. A clear trend in the ratios was seen, the ratios being abnormal with severe villous atrophy but reverting progressively to the control range with diminishing villous atrophy. Only two of six children with partial villous atrophy had ratios in the abnormal range.

DIETARY COMPLIANCE STUDY

Fig 3 shows the results in nine children, initially with subtotal villous atrophy, treated by gluten withdrawal. In the six children shown independently by dietary records to have complied with the diet, mannitol:lactulose ratios returned to normal. In the three children in whom gluten elimination was not complete, ratios remained in the abnormal range.

In five children being treated as 'coeliac' with a gluten free diet who had normal jejunal mucosas and mannitol:lactulose ratios, gluten challenge resulted in ratios falling below the lower limit for controls (fig 4). The ratios remained subnormal until the post gluten challenge biopsy specimen, which showed that subtotal villous atrophy had been caused in all five. On subsequent gluten withdrawal, ratios returned to the normal range in all five children. In three other 'coeliac' children challenged with gluten, both the ratio and mucosal structure remained normal throughout the whole of the challenge periods of 28–32 weeks (not shown)

Discussion

Mannitol and lactulose were selected as permeabil-

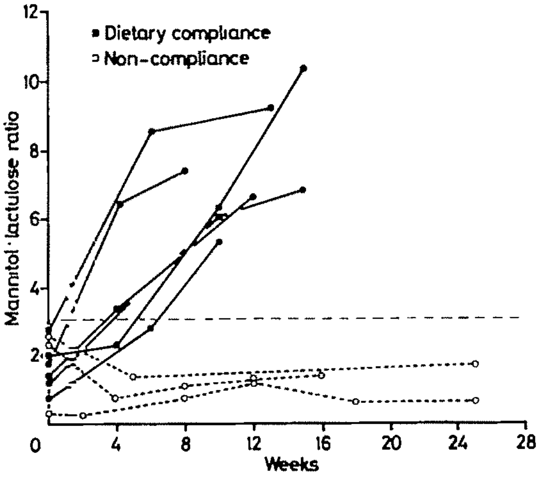

Fig 3 *Mannitol:lactulose ratios during gluten withdrawal in nine children initially with subtotal villous atrophy. The broken line denotes the lower limit of the control range defined by the mean −2SD of the* log_{10} *transformed control mannitol:lactulose ratios*

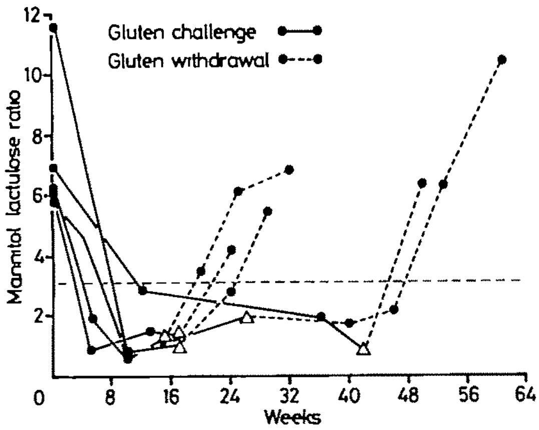

Fig 4 *The change in mannitol:lactulose ratios during a gluten challenge and after subsequent withdrawal All the children had a histologically normal mucosa on starting the challenge. △ denotes a post gluten challenge biopsy specimen showing subtotal villous atrophy The broken line denotes the lower limit of the control range defined by the mean -2 SD of the $\log_{10}$ transformed control mannitol: lactulose ratios.*

ity markers because they fulfill many of the criteria for a satisfactory test molecule.[3 4] They are constituents of normal infant diet, are present in proprietary infant milk formulas, and both have already been used in studies in preterm neonates[8] and infants.[9 10] They are not modified in the gut lumen[17 18] or in the body and although some metabolism of mannitol occurs in the liver, it is insignificant.[19] Both molecules are excreted by the kidney with clearances similar to creatinine.[18] Excretion is therefore directly proportional to the quantity crossing the mucosa of the small intestine.

The urine collection period of three hours was based on the results of a preliminary study (unpublished) which had shown that a three hour collection produced a better discrimination between normal and severely damaged mucosa patients than the more conventional five hours collection. The abbreviated test period and consequent reduction in the period of fasting is particularly advantageous in children.

The correlation of the mannitol:lactulose ratio with body surface area was an interesting finding. Previous workers have used a standard sugar dose for all body sizes[10 13] and it is possible that our body surface area related dose had the opposite effect to that intended—that is, to eliminate any body size effect. This observation suggests that the ratio of sugars ingested and the gut permeability to the sugars are not the only factors influencing the excreted sugar ratio. Gut permeability may change with age but it seems more likely that the absorption kinetics of the two sugars changes differently with dose quantity or volume or size of subject This feature warrants further investigation.

The sensitivity of the test for detecting an enteropathy was only acceptable when there was subtotal or severe partial villous atrophy (95%). Sensitivity fell to 33% for partial villous atrophy and to 25% for mild patchy villous atrophy. The test did not detect jejunal abnormalities characterised by increased cellularity only. In the control group, only one mannitol:lactulose ratio fell below the lower limit of the control range defined by the mean -2SD giving a specificity of 98%. Mannitol: lactulose ratios, however, remained in the control range in many children with an appreciable degree of villous atrophy or histological change As a screening procedure therefore, the dual sugar absorption test, in the form that we have used, will only identify the most severe degrees of villous atrophy In contrast, jejunal biopsy, with conventional histology, shows all degrees of structural damage and also provides information on the likely aetiology. Confirmation of a suspected enteropathy must still therefore depend on biopsy of the jejunum.

Many factors such as the ratio of the ingested sugars, the osmolarity of the test solution, size of the subject, and the duration of the urine collection alter the urinary ratio of the ingested sugars Furthermore, the analytical methods and the individual sugars used have varied from one study to another Few of the data already published therefore are directly comparable. The same applies to comparisons between published reports and our data. We are not aware, for example, of any other group that has used the advantage of the shorter, three hour urine collection that we report Most other workers report ratios on five hour urine collections.[6 7 10 11 13] We have also chosen to use a mannitol:lactulose ratio rather than a lactulose: mannitol ratio. There is no theoretical basis for expressing the ratio with either sugar as enumerator so for practical reasons we have expressed our results as mannitol:lactulose ratios. As the test is likely to be used in a routine clinical context, we consider it better to produce whole numbers that will be more readily appreciated in magnitude and discriminatory function. In addition, the fractional decimal numbers produced by a lactulose:mannitol ratio are more likely to cause transcription errors.

Other workers have expressed the excretion of test sugars as a percentage of the ingested dose before calculating the urinary sugar ratios. Expressed in this way, the overlap of mannitol: lactulose ratio data between our control and study groups was increased compared with the use of simple urinary concentration ratios, so no advantage was obtained. The overlap also appeared to be greater than that found by other workers.[6 7 13 14] This may have been due to our use of iso-osmolar sugar solutions but, for reasons already discussed, such comparisons are difficult and may not be valid.

The permeability of the small intestine to lactulose is known to be increased in the presence of hyperosmolar solutions.[20 21] This phenomenon occurs both in the normal and in the severely damaged jejunal mucosa.[20] The increase in permeability in the damaged mucosa is greater than that of the normal mucosa, thus increasing the separation between the two groups. This has been the rationale for using hyperosmolar solutions in adults[5–7] and moderately hyperosmolar solutions in children.[13 14] Hyperosmolar solutions do however, have the potential risk of inducing osmotic diarrhoea in children with an already damaged jejunal mucosa. We therefore considered their use unjustifiable in children. Others working with children have also chosen iso-osmolar test solutions.[10 22] The high degree of sensitivity and specificity that we report (fig 2) in the presence of severe villous atrophy did not produce complete separation of the two groups, and segregation was not improved when the results were expressed as percentage mannitol:lactulose ratios. We cannot therefore recommend the test in the present form as a screening procedure for enteropathies. Further studies evaluating the safety and usefulness of hyperosmolar solutions in children are required.

In the longitudinal studies the data from the children on gluten free or gluten challenge regimes suggested an important role for the test. The changes in the mannitol:lactulose ratio from normal to abnormal, and the reverse, were consistent throughout with the dietetic record and biopsy data. A change in bowel habit occurred in only one of the five children on gluten challenge that responded with mucosal relapse so that the change in ratio to subnormal levels was the sole indication of mucosal damage in the remainder before biopsy. The three children challenged with gluten, who did not respond in the challenge period with a change to subnormal ratios, did show a lesser initial decrease but remained within the control range. The importance of this small initial change is not known but may become apparent during the two year follow up on a normal diet necessary for exclusion of coeliac disease.

In the children with subtotal villous atrophy treated with a gluten free diet, only those not practising complete gluten exclusion failed to respond with mannitol:lactulose ratios returning to normal values within four to 12 weeks.

The value of the test therefore is much greater in longitudinal studies in an individual patient where the importance of the mannitol:lactulose ratio does not depend on its absolute value but on its relation to the results of earlier tests. A recent report has described the use of a mannitol-lactulose test, similar to ours, for following the improvement in ratio which accompanied the resolution of diarrhoea in children in the Gambia.[22]

The mannitol-lactulose dual sugar absorption test, using a sugar dose osmolarity appropriate for children with diarrhoeal disease, is not sufficiently sensitive to detect lesser degrees of villous atrophy and is not therefore a satisfactory screening procedure for an enteropathy. It may, however, have a useful role in the assessment of dietary compliance in children on a gluten free diet, and for determining the appropriate time for post gluten challenge biopsy. Its role in the sequential study of other lesions of the small intestinal mucosa deserves further study.

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Recent results of treatment of infantile hypertrophic pyloric stenosis

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SUMMARY During the five year period December 1980 to November 1985, 106 infants with hypertrophic pyloric stenosis were treated. There were no operative deaths, but two late deaths occurred from associated abnormalities. The combination of preoperative rehydration, skilled anaesthesia, and the use of the Fredet-Ramstedt operation (pyloromyotomy) have virtually eliminated mortality from uncomplicated infantile hypertrophic pyloric stenosis. The most common complications were gastro-oesophageal reflux in 11 (11%), perforation of the duodenal fornix in nine (8%), and wound infection in five (5%); no wound dehisced.

Several authors[1-3] have suggested that infants treated for hypertrophic pyloric stenosis in Britain still have unacceptably high complication rates compared with those treated in the United States, where experts have criticised British results.[4] Recent results at this hospital have been analysed to ascertain where improvements could be made.

Patients and methods

Between December 1980 and November 1985, 106 consecutive infants with pyloric stenosis were treated by one surgical team at this hospital; three were lost to follow up. Other serious associated anomalies necessitated the admission of four boys and eight girls (table 1) who will be discussed separately, but the remaining 72 boys and 19 girls (tables 2 and 3) were treated primarily for hypertrophic pyloric stenosis. In 85 of the 91 infants the diagnosis was made clinically,[4 5] but 12 infants underwent barium meal examination even though a pyloric tumour could be felt in six of them.

In all infants oral feeding was discontinued, a nasogastric tube was passed, and the stomach emptied. Milk curds were removed by lavage with warm saline. An intravenous infusion of 0·18% saline in 4% dextrose was given, and hypokalaemic alkalosis was corrected with 0·9% saline containing 10 mmol of potassium chloride in each 500 ml of saline. Infants judged to be dehydrated by more than 15% were given 30 ml/kg of plasma. Operation was performed on the next available list. To avoid unnecessary delay operations were occasionally

Table 1 *Associated abnormalities in 103 infants with pyloric stenosis*

Abnormality	*No of infants*
Major abnormalities	
Oesophageal atresia	5*
Intestinal malrotation	4
Oesophageal atresia and intestinal malrotation	2
Necrotising enterocolitis	1*
Minor abnormalities	
Meckel's diverticulum	1
Inguinal hernia	6
Undescended testis	2
Vesicoureteric reflux and urinary infection	1
Cardiovascular	3

*Include two late deaths

Table 2 *Possible predisposing factors in 91 infants presenting with hypertrophic pyloric stenosis*

	No of infants
Boys	72
Girls	19
Firstborn boys	7
Premature babies	6
One of twins	2
Family history of pyloric stenosis *	
Boys	5
Girls	5

*Includes three siblings from one family, and two sisters from another.

Table 3 *Factors associated with diagnosis of 91 infants treated primarily for hypertrophic pyloric stenosis*

	No
Mean (range) age at onset of symptoms (days)	27 (0–75)
Mean (range) birth weight (g)	3079 (1200–4390)
Weight	
Gained	76
Maintained birth weight	3
Lost	12
Palpable pyloric tumour	85
Preoperative barium meal examination	12

performed during weekends, but they were never done as emergencies

One patient underwent operation under local anaesthesia for religious reasons, but the remainder had general anaesthesia with endotracheal intubation. Infants were extubated when fully awake.[6] Opiate analgesics were not prescribed because infants of less than 46 weeks' gestational age (full term plus six weeks) have an appreciable risk of postoperative apnoea.[7]

A modification of Robertson's gridiron incision[8] was used in all but the infant having the operation under local anaesthesia. In earlier cases the hypertrophied muscle was split using either mosquito artery forceps or a Denis Browne pyloric spreader; more recently the surgeon simply turned the scalpel in his hand and used the rounded end. The handle of the Swann-Morton scalpel makes an excellent split in the pylorus without risk of damage to the duodenal mucosa. If the parents consented the appendix was removed by the inversion technique (which avoids bacterial contamination of the operative field and does not predispose to intussusception provided the appendix is devascularised).[9] Two infants underwent inguinal herniotomy during the same operation. The muscles of the abdominal wall were closed with 000 polyglycolic acid, and the same suture was used as a subcuticular stitch. Dressings were not used.

To prevent hypoglycaemia, the intravenous infusion of 0·18% saline with 4% dextrose at 2–3 ml/kg/hour was continued until the infant was feeding normally.[6] The timing of the reintroduction of feeds was left to the discretion of the nurse in charge of the ward, and no specific regimen was used. Nearly all the operations were performed during afternoon operating sessions so feeding usually began late the next morning. In nine infants the duodenal mucosa was breached so the nasogastric tube was retained for 24 hours and feeds omitted during that time.

Results

Pyloric obstruction was relieved in all infants, and none required reoperation. There were no operative deaths and no deaths among those without serious associated abnormalities. In nine infants the duodenal fornix was perforated by surgeons in training using artery forceps or muscle spreaders. In each case the duodenum was oversewn with 0000 chromic catgut and patched with omentum, and all recovered uneventfully. This complication has not occurred since artery forceps and spreaders were abandoned in favour of the scalpel handle. One infant had a severe reactionary haemorrhage requiring blood transfusion and developed an abscess (pus from which grew *Staphylococcus aureus*) at the drip site. There were four wound infections, three of which required treatment with antibiotics; *S aureus* was isolated from two of these. There were no wound dehiscences, and no incisional hernias had developed by follow up at three months. Prolonged follow up was thought unnecessary and to date none of the infants has returned to this hospital for repair of an incisional hernia.

The first postoperative feed was at a mean of 21 hours (range 4–84) after operation, and patients were sent home a mean of 76 hours (range 22–168) after operation. Those with iatrogenic duodenal perforations were in hospital for about 18 hours longer than the others (mean 94 hours, range 70–122) but the main reasons for prolonged hospital stay were associated gastro-oesophageal reflux, and wound infection. Some babies were not collected promptly by their parents.

Postoperative vomiting occurred in half the infants, and usually lasted two or three days. Vomiting persisted in nine of the 91 infants without other serious abnormalities, and all of these had barium meal examinations; six were shown to have severe gastro-oesophageal reflux. Sliding hiatal hernias were present in three of these, but only one had oesophagitis at endoscopy. All recovered spontaneously after several weeks.

Seven infants presented with oesophageal atresia, two of whom also had intestinal malrotation (table 1). One girl had Royer's syndrome[10] with associated intestinal malrotation, and she developed a wound infection with *S aureus* Two of the infants with intestinal malrotation failed to stop vomiting despite the Ladd's and Ramstedt's procedures, and one underwent Nissen fundoplication at the age of 18 months These infants obviously stayed in hospital much longer than those with isolated pyloric stenosis.

Associated anomalies caused two late deaths. A girl had birth asphyxia, colonic perforation from necrotising enterocolitis, and developed pyloric

Table 4 *Percentages of postoperative complications in reported series from the United States and Great Britain*

Authors	*Mortality*	*Mucosal perforation*	*Wound infection*	*Wound dehiscence*	*Incisional hernia*	*Bleeding*
United States						
Pollock *et al*, 1957[4]	1·0	0·5	3·0	2·0	0	1·0
Benson and Lloyd, 1964[14]	0·6	2·1	4·9	0·09	0·09	0
Bell, 1968[13]	0·22	3·0	0·3	0·3	0	0
Schärli *et al*, 1969[16]	2·5	1·2	1·6	0·4	0	0·4
Gibbs *et al*, 1975[15]	0	0·8	0·8	0	0	0
Great Britain						
Prosser, 1965[7]	0·3	0·7	0·7	0	0	0
Dougall, 1969[19]	0·5	3·5	14·0	1·5	3·0	0
Bristol and Bolton, 1981[1]	0	11·5	9·0	3·8	0	0
Caile and Davidson, 1985[3]	0	7·2	9·5	0·4	0·4	0·8
Present series	0	8·5	4·7	0	0	0·9

stenosis during recovery. Despite pyloromyotomy she never fed normally and became profoundly retarded. She died shortly after returning to the referring hospital. Another girl was originally treated elsewhere for oesophageal atresia, never fed orally, and was referred to our care at the age of 6 months. Pyloric stenosis was diagnosed and treated, but numerous operations were required for complications of the oesophageal repair. She died suddenly and inexplicably after colonic replacement of the oesophagus at the age of 3 years.

Discussion

The development of the treatment of pyloric stenosis has been well recorded.[11–13] For many years excellent results have been reported for the Fredet-Ramstedt operation from the United States,[4 11–16] but—outside selected centres[17–19]—inferior results have been recorded in Britain.[1 2] As late as 1945, mortality as high as 25% was being reported in Britain.[18] Death from pyloric stenosis alone should not occur,[14] but occasional deaths are attributed either to anaesthesia or operation.[20]

Projectile non-bilious vomiting is said to be the hallmark of pyloric stenosis,[4 13] but in our experience the nature of the vomiting is rarely helpful in diagnosis projectile vomiting has also been described in infants with gastro-oesophageal reflux, and non-projectile vomiting in those with pyloric stenosis.[1] In the absence of a palpable tumour diagnosis may be difficult, and paediatricians usually request barium meal examination. In the past some authorities[13] have recommended radiological examination in all cases; now that the dangers of neonatal irradiation are appreciated, however, most experts condone radiological diagnosis only in difficult cases[11] though barium studies are often equivocal when there is clinical doubt.[18 21] Shopfner *et al*[22] were erroneously credited with the pronouncement 'no palpable tumour—no surgery', a policy that causes unnecessary delay.[1 21] Radiological help was requested by the surgeons for only one patient in this series, but contrast meals had been performed in 11 cases by referring paediatricians.[16] In other series, between 3 and 25% of infants were submitted to radiological examination.[1 14 16 19] Ultrasound examination is popular now,[23] but in our experience is unreliable when there are serious doubts about the clinical signs.

Preparation for operation need not be hurried,[12 13 17] and most clinicians use intravenous fluid replacement,[6] though some prefer oral rehydration.[13] Of our patients, 95% were mildly dehydrated, 3% moderately so, and only one infant severely so.[3 24] Operation was always done within 48 hours of admission, and usually within 24 hours.[1 12 14 18 19 24] Respiratory depression or arrest are serious postoperative complications that may be caused by inadequate rehydration before operation.[1] Fluid and electrolyte imbalance also predispose to postoperative shock and convulsions.[6 16 24] It is essential to guard against hypothermia during the operation, and the effects of muscle relaxants and anaesthesia must be reversed before the endotracheal tube is removed.[6]

A vertical incision should be avoided because the scar becomes increasingly obvious as the child grows,[4 13] especially if a paramedian incision has been closed with tension sutures. The skin of the hypochondrium in the infant migrates superiorly and comes to lie over the lower chest in the adult, so an unusually high transverse subcostal incision in a neonate may give rise to an ugly thoracic scar in adolescence. Wound dehiscence after pyloromyotomy used to be fairly common (table 4), and remains so in those undergoing operation under local anaesthesia.[1 2] Tension sutures[3] are unnecessary with Robertson's incision, which rarely dehisces.[5,25] Skilled general anaesthesia provides ideal operating conditions permitting the routine use of Robertson's incision by junior surgeons, but it is extremely difficult to operate through a small gridiron incision without adequate muscle relaxation.[1] During the period of our review two infants (originally operated upon elsewhere) had their wounds resutured.

Some experts in Britain are extremely critical of a surgeon who perforates the duodenal fornix, but this has not been an important complication in this series.[1,6] It is more common for a timid surgeon to perform an incomplete pyloromyotomy necessitating reoperation than it is for a bold one to cause serious postoperative complications by making a small hole in the duodenum—as long as this is recognised immediately and treated appropriately.[4,13] During the period of our review two infants, not included in our results, were referred for repeat pyloromyotomy after unsuccessful operations elsewhere.

Postoperative care in hospital need not be prolonged,[14,15] and Prosser aimed at discharging his patients the next day, although the average postoperative stay was 52 hours. Prolonged hospital stay is caused by complications that occur in 10–20% of infants.[2,16] Serious haemorrhage after pyloromyotomy tends to be played down and many authors suggest that no steps need be taken to control the bleeding, though such laxity has been criticised[15] and deaths from haemorrhage have been recorded.[4] Appreciable postoperative bleeding occurs in up to 7·5% of patients[16,19] and after our salutary experience with one serious haemorrhage we have taken greater steps to secure haemostasis.

In the past, about three quarters of the deaths were caused by infection, including pneumonia, peritonitis, and septicaemia. Gastroenteritis also used to be a major cause of death or morbidity,[16,22] but none occurred in our patients. Wound infection is a common complication (table 4), and recent reports from Britain give rates of about 10%.[1–3] Organisms gain access to the wound from the umbilicus.[25,26] We excluded the umbilicus from the wound with an adhesive drape[25] but still had an infection rate of 5%. The commonest organism to be isolated is *S aureus*[2,25] so it has been suggested that antistaphylococcal antibiotics should be given shortly before operation. In our series the wound infection rate was unaffected by duodenal perforation or inversion appendicectomy.

Postoperative vomiting occurs in 30 to 95% of infants,[1,3,4,12,13,15,17,27–29] and may be attributed to preoperative oesophagitis[28] or to the use of general anaesthesia,[1] though the latter has been disputed.[2,3] Vomiting is to be expected for two to three days[4] and it is known that gastric emptying is inefficient for the first 18 hours after operation,[27] so early feeding should be avoided. Numerous feeding regimens have been used to overcome this problem[4,14,17] including delayed feeding,[28,29] but none has been completely successful. Like Prosser[17] we adopt a pragmatic approach and attach little importance to vomiting during the first 48 hours after operation. Of more importance is the vomiting that persists for several weeks after adequate pyloromyotomy.[28] Forshall[30] was one of the first surgeons to recognise the association between pyloric stenosis and incompetence of the lower oesophageal sphincter. Symptomatic gastro-oesophageal reflux occurs in 10 to 13% of patients.[30,31] The postoperative barium meal examination is helpful in the diagnosis of reflux, but of little value in the assessment of the pylorus because the radiological appearances of stenosis may persist for many months.[27,32]

Nowadays the prognosis for infants with pyloric stenosis depends on the associated anomalies, which are present in 6 to 20% of patients.[1,3,14,16,33] The association with oesophageal atresia is well known[4,6,14,33,34] but sometimes difficult to establish without radiological help, especially in those with a gastrostomy. The association with rectal agenesis[4] or Hirschsprung's disease[18] is less well known, as is that with cleft lip and palate,[16] which makes feeding difficult. Congenital heart disease is an occasional association,[4,15,16] and two of our patients underwent successful aortic valvotomies. Minor renal anomalies have been detected in up to 20% of patients,[34] undescended testis in 3%, hypospadias in 0·9%, and inguinal hernia in up to 10%.[15] Of our 103 patients, six had already undergone inguinal herniotomy, but the explanation for this association is not apparent.[34] We have observed that infants with these minor anomalies commonly vomit for several days after operation and, of the nine infants with persistent postoperative vomiting, two had had inguinal hernias repaired and one girl had vesicoureteric reflux causing urinary tract infection. Intestinal malrotation was an important association in our series, though this has been reported infrequently in the past.[16,18,35]

Our results could have been improved by ensuring that the pylorus was split with a blunt instrument, by greater attention to haemostasis, and by more vigorous attempts to prevent wound infection, possibly by using prophylactic antistaphylococcal antibiotics. Fewer contrast radiographs should have been done, and postoperative vomiting should have been anticipated in infants with minor associated anomalies. Uncomplicated cases should have been discharged within 48 hours of operation. Infants with major associated anomalies should be treated in regional centres, and otherwise healthy infants being treated in district general hospitals should be treated by surgeons and anaesthetists with a special interest in paediatric surgery.[1]

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Neonatal seizures: the Dublin Collaborative Study

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SUMMARY Asphyxial seizures occurred in 89 of 101 829 infants born alive at term (0·87/1000) in three large maternity hospitals from January 1980 to December 1984. These seizures were significantly associated with antenatal complications, primiparity, and prolonged pregnancy. Meconium staining of the amniotic fluid was also associated with asphyxial seizures, but there were high false positive (11%) and false negative (50%) rates. Fifteen of the infants who had seizures died (18%) and 21 (25%) were handicapped at 1 year. Outcome was most successfully predicted by the way the infant was feeding at 1–2 weeks. All infants taking more than half their estimated requirements by mouth at 1 week were normal, and those still being fed by tube at 2 weeks were handicapped.

Asphyxia is the commonest cause of brain injury in the perinatal period. Prevention, particularly in infants born at term, is the major goal of perinatal care. Perinatal asphyxia has been variously defined as including intrapartum events such as abruptio placentae, accidents with the cord, abnormal patterns of fetal heart rate, low fetal scalp pH, and the passing of meconium by the fetus. Definitions have also included assessments of the infant's poor condition at birth such as the need for and the duration of resuscitation, the Apgar score, the acid base measurement, and varying combinations of abnormal neurological signs including seizures.

Many of these indices correlate poorly with both proven intrapartum asphyxia (hypoxia, acidosis, and ischaemia) and with brain damage among survivors.[1–4] A seizure occurring within 48 hours of birth in an infant born at term is the most rigorously validated event that reflects asphyxia that can be prevented by better obstetric technique. Such seizures are also the most strongly predictive of either neonatal death or survival with handicap.[5 6] In this study, which was carried out in three large maternity hospitals, we attempted to document the incidence and outcome of neonatal asphyxial seizures with a view to predicting and therefore preventing them. By identifying reliable prognostic factors in the immediate neonatal period, we hoped to counsel parents more accurately.

Patients and methods

The study population comprised all infants born alive at more than 37 completed weeks' gestation in the Coombe, the National, and the Rotunda maternity hospitals during the five years January 1980 to December 1984. Seizure was diagnosed when the consultant paediatrician found evidence of one of the following: myoclonic, multifocal clonic, generalised tonic, or focal clonic seizures. Infants with subtle seizures or 'jitteriness' were excluded. All infants were observed daily for at least four days postpartum, and those causing concern were seen daily by a consultant. Infants suspected of having seizures were admitted to the neonatal intensive care unit for assessment including estimations of blood glucose, sodium, and calcium concentrations; full blood count; lumbar puncture, neurological examination, and (latterly) cranial ultrasound examination. Infants of 37 weeks' gestation or more whose perinatal history suggested seizure due to intrapartum asphyxia and who had a fit within 48 hours of delivery were included in the study. All three hospitals collect data prospectively on infants with asphyxial seizures, which are presented at a monthly perinatal morbidity conference. The next normally formed infant of the same gestational age born after each infant who had a seizure was used as the control. Data about outcome of survivors was obtained up to a minium of one year from the records of the developmental follow up clinics at each hospital A poor outcome among those who had seizures was defined as death, or handicap including cerebral palsy, mental retardation, epilepsy, or hearing or visual deficit

Antenatal variables documented in index cases and controls included maternal age, height, weight, weight gain in pregnancy, parity, incidence of cigarette smoking, and specific obstetric complications (hypertension, proteinuria, and antepartum haemorrhage). Intrapartum variables analysed included spontaneous or induced onset of labour, oxytocin stimulation, meconium stained amniotic fluid, fetal heart rate (monitored either by intermittent auscultation or by continuous electronic monitoring), mode of delivery (normal, instrumental, or caesarean), and gestational age.

Neonatal variables recorded were sex, birth weight, Apgar score, need for intubation or resuscitation, and interval to the onset of the first seizure. Management of infants with seizures was similar in all three hospitals and included treatment with phenobarbitone (10–20 mg/kg), phenytoin (10 mg/kg) and diazepam (0·1 mg/kg); prophylactic anticonvulsant drugs were not given.

In order to assess the prognostic significance of methods of feeding, infants were assigned to one of three groups (assuming a requirement of 150 ml/kg/day of milk): those taking at least half their requirements orally by 1 week of age; those taking at least half their requirements orally by 2 weeks of age, and those who were still receiving more than half the daily requirements by nasogastric tube at 2 weeks of age. The χ^2 test was used to estimate the significance of differences in proportions.

Results

During the study period a total of 101 829 infants were born alive after more than 37 completed weeks' gestation; asphyxial seizures occurred within 48 hours of birth in 89 (0·87/1000). These were compared with 88 control babies. The antepartum variables that were significantly associated with the development of seizures are shown in table 1. There was no association betweeen the development of seizures and either cigarette smoking or weight gain of less than 10 kg during pregnancy.

The intrapartum variables that were significantly associated with the development of seizures are shown in table 2. Meconium staining did not occur in half the babies with seizures though it was found in 11% of the controls and those who had seizures were more likely to be born by emergency caesarean section or with the assistance of forceps than control babies. There was no association between induction of labour and development of seizures.

The babies who had seizures weighed significantly less at birth than controls (table 2) but when the neonatal data of those who had seizures were analysed with regard to outcome (table 3), the association

Table 1 *Comparison of antenatal details between the groups*

	Babies with seizures (n=89)	*Control group (n=88)*	*p Value*
Maternal age			
<20	8	5	NS
20–24	21	34	NS
25–29	27	20	NS
30–34	16	22	NS
≥35	17	7	<0·05
Parity			
0	49	36	<0·05
1–4	27	40	NS
>4	13	12	NS
Complications	34	15	<0·01
No complications	55	73	NS

Table 2 *Comparison of intrapartum details and birth weight between the groups*

	Babies with seizures (n=89)	*Control group (n=88)*	*p Value*
Amniotic fluid stained with meconium	44	10	<0·001
Emergency caesarean section	24	4	<0 001
Mid or high cavity forceps delivery	24	9	<0·001
Gestation longer than 41 weeks	24	6	<0·001
Birth weight (g):			
<3000	25	12	<0·05
3000–3500	35	32	NS
>3500	29	44	NS

Table 3 *Association between measurements and outcome in 89 babies who had seizures*

	Good outcome	*Poor outcome*	*p Value*
Feeding (n=66):			
No taking half feeds orally by 7 days	25	0	<0·001
No taking half feeds orally between 7 and 14 days	22	9	NS
No requiring tube feeding for >14 days	0	10	<0·01
No intubated at birth (n=50):			
<10 minutes	14	4	NS
≥10 mintues	10	22	<0·001
Apgar score at one minute (n=84):			
≤5	34	32	<0·05
>5	14	4	NS
Apgar score at five minutes (n=84)			
≤5	9	22	<0·001
>5	39	14	NS

between low birth weight and poor outcome did not reach significance. Not surprisingly low Apgar scores at one minute ($p<0\cdot05$) and 5 minutes ($p<0\cdot001$) and the need for intubation for longer than 10 minutes at birth ($p<0\cdot001$), were significantly associated with a poor outcome, but the age of occurrence of seizures was not. In 66 infants the method of feeding at 1 and 2 weeks of age was documented; all infants who were satisfactorily feeding orally at 1 week were normal, and all those requiring tube feeding at day 14 were abnormal ($p<0\cdot001$).

Of the 89 infants who had seizures 15 died (18%), 21 survived but with handicaps (24%), and five were lost to follow up (all five were in the group who had rapidly returned to normal within the first week, four of whom have also been normal at six weeks, one did not attend). About a third of the surviving infants were handicapped.

There were significant differences among the rates of seizures among the three hospitals (table 4), as well as in the proportion of infants of 42 weeks' gestation or more in the seizure group (0 to 60%). This may reflect differences in the populations but must also reflect different management policies. The suggestion finds some support in the significant differences among the three hospitals in the number of caesarean sections performed ($p<0\cdot001$), the number of induced labours ($p<0\cdot001$), and the number of forceps deliveries ($p<0\cdot001$). Among the infants born at more than 41 weeks' gestation who developed seizures ($n=24$), seven (29%) had a poor outcome compared with 29 of 65 infants born at term (45%); this was not significant.

Discussion

Developments in perinatal medicine over the past decade have largely concerned the prevention of perinatal asphyxia and the more rigorous assessment of the association between preventable asphyxia and the incidence of long term brain damage—for example, cerebral palsy.[3 4] Given that many of our assumptions regarding the causes of cerebral palsy, mental retardation, and epilepsy are based on outdated knowledge[1] and that there are many different definitions of perinatal asphyxia in current use, it is not surprising that confusion exists about the perinatal prevention of handicap. In addition, the introduction and widespread use of continuous fetal heart rate monitoring in labour has been justified by claims that it halves perinatal 'morbidity'[7] despite the fact that we have no reliable estimate of how many complications originate in the perinatal period nor how many are really preventable.

Of the various definitions of intrapartum asphyxia currently used including abnormalities of the fetal heart rate, low fetal scalp blood pH, and meconium staining of the amniotic fluid, not only are none strongly predictive of the condition of the baby at birth but their association with long term outcome is unknown.[2 3 8 9] Of the various methods of defining 'poor condition at birth' (birth asphyxia), both a low Apgar score and the need for intubation (but not acid base measurement) have been shown to be only weakly predictive of long term handicap.[10–14]

The randomised controlled trial of intrapartum fetal heart rate monitoring carried out in Dublin[5] was the first clinical study large enough to allow assessment of the validity of these various indices of perinatal asphyxia. This study strongly supported the hypothesis that neonatal seizures within 48 hours of delivery reflect intrapartum asphyxia. There were no significant differences between the monitored and unmonitored groups for abnormal neurological signs (other than seizures) in the neonatal period, low Apgar score, low pH in the umbilical vein, apnoea at birth, or endotracheal intubation. Dennis and Chalmers[6] proposed that the early (within 48 hours) rate of seizures in infants born at term would provide a sensitive indicator of the quality of obstetric care, and the Dublin study of monitoring seems to support this. In addition, the fact that the incidence of seizures in the three hospitals in the present study were significantly different (0·55, 0·91, and 1·2/1000 babies born alive at term, respectively, $p<0\cdot05$) supports the hypothesis that asphyxial seizures are at least partially preventable.

The rate of seizures in the present study of 0·87/1000 babies born alive at term (43% having a poor outcome) compares favourably with other similar studies. Levene *et al* reported a poor outcome (1/1000 live births at term[14]) among

Table 4 *Incidence of seizures and obstetric interventions in the three hospitals January 1980–December 1984*

	Hospital A	*Hospital B*	*Hospital C*	*p Value*
Incidence of seizures/1000 live births	0·55	0·91	1·2	<0·05
Percentage of induced labours	22·4	10·0	9·7	<0·001
Percentage of forceps deliveries	6·8	6·3	16·1	<0·001
Percentage of caesarean sections	7·8	5·2	8·6	<0·001

The p values refer to significant differences in group rates for each variable asphyxiated infants delivered in Leicester from 1980 to 1984 and rates of 'moderate' and 'severe' postasphyxial encephalopathy of 1·15 and 1·0/1000 babies born alive at term, respectively. All the former and many of the latter group would be expected to have neonatal seizures though some would be 'subtle seizures'. Leveno *et al*[15] reported a rate of seizures of 1/1000 live births weighing more than 2500 g, and used this 'low' rate as one of the main justifications of a rate of caesarean section of 18%. The present study included five infants born at term weighing less than 2500 g, and excluded a similar number of infants who had seizures but weighed more than 2500 g and were born prematurely. MacDonald *et al*[5] showed that 93% of infants of more than 28 weeks' gestation who develop asphyxia seizures do so within 48 hours of delivery. That one hospital in this study had a rate of seizures of 0·55/1000 babies born alive at term with a rate of caesarean section of 8% means that prevention of intrapartum asphyxia does not depend on the number of caesarean sections. This hospital had a high rate of induction of labour (22%) directed at prevention of prolonged pregnancy, and used continuous monitoring of the fetal heart rate in 33% of labours in pregnancies at term. This raises the question of whether continuous monitoring of the fetal heart rate prevents asphyxial damage. In the trial of intrapartum monitoring a significant reduction in asphyxial seizures occurred in the group that was monitored, though this effect was confined to the 15% of labours that lasted more than five hours. Length of labour was not included in the present study as it was felt that the retrospective assessment of onset and duration of labour was insufficiently accurate.

In infants born at term asphyxial seizures have been shown to reflect preventable obstetrical intrapartum asphyxia in a prospective randomised trial.[5] The present study confirms the association between asphyxial seizures and poor outcome (42%) and we are now able to counsel parents on the likelihood of handicap using the infant's neurological state and the ability to feed normally as guides.

Asphyxial seizures should be identified as well as asphyxial deaths (before and during labour, and in the neonatal period) in all maternity units because they are a sensitive indicator of the value, or otherwise, of perinatal intervention.

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Neurodevelopmental outcome of babies weighing less than 2001 g at birth: influence of perinatal transfer and mechanical ventilation

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SUMMARY From 1976 to 1980, 1034 children who had weighed less than 2001 g at birth were cared for at the North Western regional neonatal intensive care unit. Of these, 315 babies were neonatal referrals and 91 were born in the unit after antenatal transfer from their district hospital. Significantly fewer of the babies referred as neonates survived (n=167, 53%) compared with 67 of the antenatal referrals (74%), and 490 of those born in the unit (78%). They also had a higher incidence of major handicaps (24 of 167, 14%) compared with six of 67 (9%) of the antenatal referrals and 35 of 490 (7%) of those born in the unit. To control for selection bias among neonatal referrals, the outcome of ventilated neonatal referrals was compared with that of ventilated babies born in the unit. The two groups were comparable for the incidence of a wide range of neonatal complications. No differences in rates of survival or handicap were found. We conclude that sick babies transferred after birth to regional neonatal intensive care units have similar short and long term outcomes to sick babies born in regional units.

From 1976–80 this hospital was the sole referral centre for intensive care of newborn infants in the North Western region. At its inception the neonatal referral service was directed towards the transport of babies deemed to require mechanical ventilation. During the same period an antenatal referral service evolved for the transfer of mothers with high risk pregnancies in which the need for neonatal intensive care was anticipated. In this paper we report the mortality and long term neurodevelopmental morbidity of low birthweight babies transferred in the perinatal period to our hospital, and relate these outcomes to the need for ventilatory support.

Patients and methods

We studied 1034 infants who were born alive weighing 2000 g or less between 1 January 1976 and 31 December 1980 who were cared for on the neonatal medical unit at this hospital Mortality and neurodevelopmental outcome were analysed for three groups: babies who were referred as neonates (n=315), antenatal referrals (n=91), and babies who were born to mothers who booked for delivery at this hospital (n=628). The 'ventilated' subgroup comprised 386 babies who received more than four hours mechanical ventilation through an endotracheal tube.

NEONATAL REFERRALS

The organisation of the neonatal referral service in the North Western region has been described previously.[1] Babies were transferred from 18 special care units (16 within the region). The median distance was 10·9 miles (range 2–100) and the median age at referral was 8·7 hours. Two hundred and eighty babies (89%) were referred within the first 48 hours and three (1%) after the 28th day. A primary respiratory illness was the reason for referral in 300 (95%) cases, prematurity alone being the indication in only two cases. No important complications developed during any of the journeys.

Details of each child's condition on arrival at the referring unit were recorded in 303 (96%) cases. Two hundred and two (67%) were judged to be in a stable condition. In the others the problems encountered were: central cyanosis (n=47), cyanosis and gasping (n=16), peripheral circulatory failure (n=31), untreated or inadequately drained pneumothorax (n=7), hypoglycaemia (blood glucose <1·5 mmol/l; n=11), and hypothermia (rectal temperature <34°C; n=27) Only 20 infants were breathing air spontaneously. Of the remainder, 149 were being given oxygen by headbox, 12 (4%) were receiving continuous positive airways pressure ventilation and 117 (37%) were receiving intermittent positive pressure ventilation, including 47 (15%) who were being hand ventilated. Thirteen children were being managed unconventionally. During transfer 212 received mechanical ventilation through an endotracheal tube, 41 received continuous positive airways pressure ventilation by face mask, and 52 were breathing oxygen spontaneously by headbox.

ANTENATAL REFERRALS

One hundred and twelve pregnancies (126 unborn babies) were transferred during the study period One infant was born during the ambulance journey, two were stillborn at this hospital, and four mothers were later returned to their referring units for delivery Thirty infants weighed more than 2000 g at birth and are not considered further.

The main indications for antenatal referral were: pre-eclampsia (25%), premature rupture of the membranes or preterm labour (40%), intrauterine growth retardation (18%), and Rh haemolytic disease (13%). No influence on survival was observed when individual indications for transfer were considered. The median interval from antenatal transfer to delivery was 10·5 days Three babies died in the delivery unit of extreme prematurity. Eighteen babies (20%) did not develop any neonatal complications and might therefore have been deemed unnecessary antenatal referrals.

Methods

Seven hundred and twenty four babies (70%) survived to be discharged home. Follow up information was obtained for 674 (93%) at a median (range) age of 3 years 3 months (2 years–6 years 9 months), including 20 children who subsequently died. Four further children died from acute neonatal illnesses after return to their referring units but before they could be discharged home. These have been classified as deaths before discharge. The details of follow up have been described previously [2] Of the survivors, 570 were examined and completed a psychometric test (NM), and information was abstracted from hospital or community follow up records for 56 other children. The parents of an additional 28 children who lived outside the north west replied in answer to a questionnaire that the children had no neurological or development problems.

For the purposes of this study we classified outcome into two groups: major neurodevelopmental handicap and normal. A major neurodevelopmental handicap comprised any of the following disabilities: cerebral palsy, developmental retardation (Griffiths quotient (GQ) or Wechsler intelligence quotient (IQ) of less than 70), blindness or deafness sufficient to warrant special schooling, and hydrocephalus

The ages at follow up were calculated from the expected date of delivery. The significances of various comparisons were tested using the χ^2 test or the Mann-Whitney U test, as appropriate.

Results

PERINATAL TRANSFER AND OUTCOME

The proportion of babies surviving to be discharged home in the three study groups is shown in table 1. Among those with birth weights of 1251–2000 g, the survival rates in antenatal referrals and those babies born in this hospital were similar (83% and 88%, respectively), whereas neonatal referrals had a significantly lower survival rate (65%). In contrast, among babies weighing 500–1250 g, the survival rates of neonatal referrals and babies born in this hospital were similar (37% and 40%, respectively), and the differences in survival among the three groups were not significant.

Sixty five survivors (9%) had a major handicap. The incidence of handicap in the neonatal referrals (14%) was greater than that in babies born in this hospital (7·1%; $p<0·001$), and this difference was

Table 1 *Survival by birth weight 1976–80*

	Birth weight					
	500–1250 g		*1251–2000 g*		*Total No <2000 g*	
	No	*No (%) of survivors*	*No*	*No (%) of survivors*	*No*	*No (%) of survivors*
Neonatal referrals	33	49(37)	182	118(65)	315	167(53)
Antenatal referrals	32	18(56)	59	49(83)*	91	67(74)†
Born in hospital	45	58(40)	483	432(89)†	628	490(78)†

*$p<0·02$, and †$p<0·001$ compared with neonatal referrals

seen among those with birth weights of 1251–2000 g ($p<0\cdot01$) but not at 501–1250 g (NS) In contrast, in each birthweight group the incidence of handicap in antenatal referrals was similar to that among babies born in this hospital (table 2). Neither differences in survival nor in the incidence of handicap varied significantly when allowance was made for congenital abnormalities.

The incidence of individual major disabilities is shown in table 3. This table excludes 10 children whose handicaps were due to major congenital abnormalities described previously.[2] Cerebral palsy and developmental delay (GQ or IQ <71) were the commonest disabilities in all three groups. None of the six survivors with major handicap who had been referred antenatally were either deaf or blind. Deafness was found in a quarter of the handicapped survivors who had been referred as neonates compared with only 4% of handicapped survivors born in this hospital ($p<0\cdot04$) Blindness was found in between 13 and 16% of the survivors in these two groups There were no significant differences in the incidences of cerebral palsy, developmental delay, or hydrocephalus among the three groups, each of which also had a similar mean number of disabilities/handicapped survivor, implying a similar degree of handicap in each group.

EFFECT OF MECHANICAL VENTILATION ON SURVIVAL AND HANDICAP

Mechanical ventilation exerted a major influence on outcome. Babies who were ventilated had a significantly lower survival rate and a higher incidence of handicap among survivors compared with the babies who were not ventilated (40% compared with 96·8%, and 18% compared with 4·7%, respectively). In addition, major differences between the study groups in their need for mechanical ventilation were found A significantly higher proportion of neonatal referrals were ventilated (77%) than antenatal referrals (37%, $p<0\cdot001$) or babies born in this hospital (24%; $p<0\cdot001$) To what extent does the need for ventilation account for the differences in outcome between the neonatal referrals and the others?

Because only a small number of babies received ventilation after antenatal transfer ($n=34$) these were included with the babies born in this hospital

Table 2 *Incidence of major handicap among survivors*

	Birth weight					
	500–1250 g		*1251–2000 g*		*Total No <2000 g*	
	No	*No (%) with major handicap*	*No*	*No (%) with major handicap*	*No*	*No (%) with major handicap*
Neonatal referrals	49	12(25)	118	12(10)	167	24(14)
Antenatal referrals	18	3(17)	49	3(6)	67	6(9)
Born in hospital	58	11(19)	432	24(6)*	490	35(7)†

*$p<0\cdot01$, and †$p<0\cdot001$ compared with neonatal referrals

Table 3 *The incidence of individual disabilities in children with major handicaps*

	Antenatal referrals ($n=6$) No (%)	*Neonatal referrals ($n=24$) No (%)*	*Born in hospital ($n=25$) No (%)*	*Total ($n=55$) No (%)*
Disability				
Cerebral palsy	4(67)	12(50)	15(60)	31(56)
GQ or IQ <50	2(33)	6(25)	5(20)	13(24)
51–70	3(50)	9(38)	7(28)	19(34)
Blindness	0	3(12)	4(16)	7(13)
Deafness	0	6(25)	1(4)	7(13)
Hydrocephalus	1(17)	5(21)	2(8)	8(14)
Mean number of disabilities/child	1·7	1·7	1·4	1·5
Associated impairments				
Fits	2(33)	4(17)	6(24)	12(22)
Clumsiness	1(17)	4(17)	1(4)	6(11)

for further analysis. In addition, we have excluded children whose death (n=36) or major handicap (n=10) were directly attributable to a major congenital abnormality, and those babies born in this hospital who were not admitted to the neonatal medical unit but died on the delivery suite (n=13). All but one of the exclusions were born in this hospital.

For ventilated babies within each birthweight category no differences in survival or incidence of handicap were found between the ventilated neonatal referrals and babies born in this hospital (table 4). Babies born in this hospital who required ventilation were more likely to have had a lower Apgar score at 1 minute (p<0·001), or to have received intubation in the delivery room (p<0·001) compared with ventilated neonatal referrals. Otherwise the incidence of a wide range of neonatal illnesses was similar between the two ventilated groups, who also received ventilation and oxygen treatment for a similar length of time (table 5).

For babies who were not ventilated, within each birthweight category no differences in survival were found between the neonatal referrals and babies born in this hospital. Among those of 1251–2000 g birthweight, however, more surviving neonatal referrals were handicapped (11% compared with 3·4% p<0·05). In contrast, for birthweights

Table 4 *Survival, and incidence of major handicap in survivors in babies who were ventilated and those who were not*

	Birth weight 500–1250 g			*Birth weight 1251–2000 g*		
	Total No	*No (%) of survivors*	*No (%) with handicap*	*Total No*	*No (%) of survivors*	*No (%) with handicap*
Babies ventilated:						
Neonatal referrals	103	30(29)	10(33)	133	73(55)	7(10)
Born in hospital	99	24(24)	8(33)	71	36(51)	4(11)
Babies not ventilated:						
Neonatal referrals	23	19(83)	2(10)	46	45(98)	5(11)*
Born in hospital	61	51(84)	4(8)	439	436(99)	15(3)

*p<0·05 compared with those born in unit

Table 5 *Comparison of frequency of perinatal events between those born in unit and neonatal referrals for babies who were ventilated and those who were not*

	Ventilated babies		*Babies not ventilated*	
	Neonatal referrals (n=236) No (%)	*Born in hospital (n=170) No (%)*	*Neonatal referrals (n=69) No (%)*	*Born in hospital (n=500) No (%)*
Apgar score <3 at 1 minute	89(38)	97(57)	15(22)	123(25)
at 5 minutes	27(11)	28(16)	2(3)	18(4)
Intubated at delivery	104(44)	118(69)***	17(25)	141(28)
Infant respiratory distress syndrome	181(77)	120(70)	44(64)	38(8)***
Congenital pneumonia	27(11)	21(12)	13(19)	27(5)***
Early apnoea (<72 hours)	19(8)	10(6)	10(14)	27(5)**
Late apnoea	34(14)	28(16)	16(23)	32(6)***
Pneumothorax	96(41)	58(34)	2(3)	3(1)
Patent ductus arteriosus	36(15)	28(16)	8(12)	12(2)***
Chronic lung disease	14(6)	9(5)	1(1)	0
Early onset of sepsis	56(24)	40(24)	18(26)	41(8)***
Late onset of sepsis	89(38)	58(34)	23(33)	74(15)**
Fits	44(19)	25(15)	4(6)	12(2)
Other abnormal neurological symptoms	60(25)	52(30)	9(13)	25(5)*
Median (range) duration of ventilation	2·1 days (1–52)	2·4 days (1–40)		
Median (range) duration of oxygen treatment	5·4 days (1–150)	6·3 days (0–563)†		

*p=<0·02; **p=<0·01; ***p=<0·001 † one baby ventilated with air for apnoea

500–1250 g similar proportions in each group survived with handicaps (table 4).

To necessitate neonatal transfer a baby must have developed a severe illness. Neonatal referrals who were not ventilated had high frequencies of adverse perinatal events compared with babies born in this hospital who were not ventilated (table 5). This is reflected in the high incidence of later handicap in the referred group.

Discussion

Geographically based studies have shown that babies who are born and cared for in a perinatal intensive care centre have significantly higher survival rates compared with babies who are born at district obstetric units, even if they are subsequently transferred.[3 4] Our observation of a higher mortality and incidence of handicap among babies transferred in the neonatal period compared with antenatal referrals or babies born in this hospital is consistent with these findings. One further study observed that intraventricular haemorrhage was more common among neonatal transfers,[5] though more recent data suggest that this may not be so.[6] We have, however, taken the analysis further by examining specific subgroups of the referred patients and those born in this hospital, according to whether or not they received mechanical ventilation. In addition, we used both survival and neurodevelopmental handicap as outcome measures, because the quality of survival is as important as survival itself.

Babies who are transferred in the neonatal period are highly preselected by the exclusion of, firstly, those who die in the first few hours after birth; secondly, those who develop no postnatal complication and, thirdly, by the exclusion of those pregnancies in which preterm delivery is anticipated and transfer to the regional centre effected. Thus in the absence of a properly randomised, controlled trial it is difficult to assess objectively the additional risk to a small baby of delivery outside the regional centre and subsequent transfer when severe neonatal illness occurs. The simple reporting of geographically based data (as has been advocated) will not answer this question.

When all babies were considered it was at first surprising that the differences in survival and handicap between neonatal referral, antenatal referral, and those born in this hospital were least marked for those in the 500–1250 g birthweight group. The antenatal referral and born in this hospital groups, however, were biased in as much as they comprised both those babies who, being extremely small, died soon after birth in the delivery room, and those babies who developed no major complications, thereby invalidating comparison with neonatal transfers.

The comparison of ventilated babies in the group referred and those born in this hospital is a logical attempt to control for preselection. The outcome for ventilated infants was clearly worse than for those who did not need such support, and a much higher proportion of neonatal referrals required ventilation Even so, the ventilated babies born in this hospital had lower Apgar scores at 1 minute and a higher incidence of intubation in the delivery room than the neonatal referrals, implying that they were in poorer condition at birth. None the less, in both ventilated groups the time course of the respiratory illness and the incidence of postnatal complications were remarkably similar, suggesting that the severity of neonatal illness was similar. When the two ventilated groups were compared no differences in survival or incidence of major handicap were observed.

Surviving neonatal referrals who were not ventilated had a higher incidence of handicap compared with babies born in this hospital and not ventilated. These neonatal referrals, however, are quite different from the other babies who were not ventilated, as they suffered from a variety of serious neonatal illnesses necessitating referral. These neonatal referrals had a much higher incidence of clinical risk factors compared with the group born in this hospital who were not ventilated (table 5), these being mostly healthy preterm babies.

Babies born in this hospital who were not ventilated and weighed 1251–2000 g formed the largest group in this study. Therefore, despite having the lowest handicap rate of any group discussed, in real terms they made a substantial contribution to handicap among infants weighing 2000 g or less, as they made up 27% of the handicapped children.

The range of disabilities encountered among survivors varied slightly between the groups, with the obvious exception that deafness was more common among survivors after neonatal transfer. The reason for this difference and its clinical significance are not clear. The cause of deafness among low birthweight survivors is uncertain and probably multifactorial.[7] This disability has not been previously associated with neonatal transfer.

Despite the striking similarities in both clinical course and outcome for the two groups of ventilated babies, however, the populations are still not identical: transferred babies were in significantly better condition at birth (table 4). There remains the possibility that lung disease among neonatal transfers may have been worsened by suboptimal care before referral, as only 67% were judged to be in satisfactory condition when they arrived. This, together with intubation for transfer, may have resulted in babies receiving long term mechanical ventilation that would not have been necessary had they been born and managed in the regional centre

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Neonatal tumours: Glasgow 1955–86

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SUMMARY Fifty one neonatal tumours were diagnosed in Glasgow over a 32 year period. The most common tumours were teratomas (n=19), others being renal tumours (n=9), soft tissue sarcomas (n=8), neuroblastomas (n=7), and others (n=8). Of the total, 31% were malignant. Neonatal tumours pose difficult problems of management, and because of their comparative rarity and the great potential for cure we recommend that all centres dealing with such patients should contribute to and benefit from a Neonatal Tumour Registry.

Tumours in neonates are rare; the incidence in the United States is 3·64/100 000 live births[1] and that in the United Kingdom is 1·70/100 000 [2] Tumours in children display many features that distinguish them from adult tumours. Neonatal tumours also form a characteristic group. Little is known about factors responsible for the development of tumours in this age group. Genetic factors have been shown to be important in the development of certain retinoblastomas[3] and a few tumours have been linked with chromosomal and congenital abnormalities.[4] Lack of normal immune response by the fetus may be important.[5] Exposure to ionising irradiation has long been recognised as a carcinogen,[6] but other environmental factors acting transplacentally probably also have an important role.[7] The aims of this study were to determine the categories of tumour seen in this age group, to determine the comparative incidence of each tumour, to assess the effectiveness of various treatments, and to see what lessons could be learned for the future

Methods

We reviewed all solid tumours occurring during the first 4 weeks of life that presented in Glasgow from 1955 to 1986. Leukaemia and tumours of the central nervous system were not included in the study Fifty one neonates presented with solid tumours: 30 girls and 21 boys. For analysis the tumours were divided into the following categories: teratomas, neuroblastomas, soft tissue sarcomas, tumours of the eye and orbit, hepatic tumours, and miscellaneous tumours as defined by the Childhood Cancer Research Group, Oxford.

Results

The results showed that 16 patients (31%) had malignant tumours and there were 34 survivors (67%). Table 1 shows the number of cases presenting over each time period during the study and the associated mortality. Table 2 shows the number of patients, those with malignant tumours,

Table 1 *Number of survivors and deaths in patients with neonatal tumours 1955–86*

	No of survivors	*No of deaths*	*Total No*
1955–60	2	0	2
1961–65	5	4	9
1966–70	2	3	5
1971–75	0	1	1
1976–80	8	4	12
1981–86	17	5	22
	34	17	51

Table 2 *Types of tumour and mortality in patients with neonatal tumours 1955–86*

Type of tumour	*Total No*	*No (%) malignant*	*No (%) of deaths*
Teratoma	19	1 (5)	4 (21)
Neuroblastoma	7	7 (100)	4 (57)
Soft tissue sarcoma	8	4 (50)	4 (50)
Renal tumours	9	0	2 (22)
Tumours of eye and orbit	4	3 (75)	0
Hepatic tumours	3	0	2 (67)
Squamous carcinoma	1	1 (100)	1 (100)
Total	51	16 (31)	17 (33)

and the associated mortality in each group. Forty of the cases (78%) presented at birth, three (6%) during the first week, two (4%) each during the second and third weeks, and four (8%) during the fourth week of life.

TERATOMAS

Eighteen of the teratomas were sacrococcygeal and one retroperitoneal. Of the sacrococcygeal teratomas, 15 occurred in girls. All except the most recent (which was diagnosed by prenatal ultrasound) were diagnosed at or soon after birth. Ten were postcoccygeal, seven both precoccygeal and postcoccygeal, and one was pelvic. The patient with a malignant sacrococcygeal teratoma was the only one who had a raised plasma α fetoprotein concentration. Of the 18, 15 (83%) survived; two died from septicaemia, and one from an intraventricular haemorrhage.

One patient had a retroperitoneal teratoma presenting with an abdominal mass. Histological examination at the initial resection showed benign tissue, but after a series of re-explorations over the next two years the patient died of metastatic carcinoma aged 3 years.

NEUROBLASTOMAS

Seven patients had neuroblastomas. Two were stage I, three were stage IVs, and two were stage IV. One localised suprarenal neuroblastoma 5 mm in diameter was noted incidentally at necropsy in a neonate with spina bifida and hydrocephalus who died of meningitis; the other survived after excision of the tumour. Operation in the stage IVs group was limited to diagnostic biopsy and, in one patient removal of the primary suprarenal tumour. All were given cytotoxic drugs, though for one this consisted of vitamin B_{12} alone, which was fashionable at the time. The only death in this group was caused by cytotoxicity, treatment having been instigated in an attempt to decrease tumour bulk that was causing respiratory distress. Both patients with stage IV disease died without receiving definitive treatment.

RENAL TUMOURS

All nine patients with renal tumours presented with abdominal masses, and all the tumours were mesoblastic nephromas. Of the seven patients who presented before 1967, the initial histological diagnosis was known in three. All were reported as malignant, and one received actinomycin D. Two patients died of early postoperative complications (both in the 1960s) including the patient who received perioperative chemotherapy. Richmond and Dougall[8] have previously reported the other four cases, all of whom were treated by simple excision of the tumour and all of whom survived. Our increased knowledge of the pathogenesis of renal tumours presenting in the neonatal period has resulted in the more recent patients being treated more conservatively, that is, by operation alone.

SOFT TISSUE SARCOMAS

There were three rhabdomyosarcomas; the first rapidly deteriorated after birth and at necropsy an extensive rhabdomyosarcoma of the bladder was found.[9] The second patient, whose mother was being treated with warfarin during her pregnancy, presented with what was thought to be a haematoma of the thigh. Confirmation of the diagnosis of rhabdomyosarcoma was obtained by xenografting a portion of the tumour, and subsequently examining it by electron microscopy. Despite aggressive treatment with cytotoxic drugs and operation the child died of metastates. The third patient, who presented with rhabdomyosarcoma of the lower limb, survived after simple excision of the tumour.

The five mesenchymal tumours were a heterogeneous group, and their management and outcome depended on the site and histological nature of the lesion. One patient presented with a left haemothorax caused by a spindle cell sarcoma in the left lower lobe of her lung. This was successfully resected and then irradiated. Although she made an excellent recovery, she presented six months later with overwhelming pneumococcal pneumonia and pneumococcal meningitis. This was presumably a result of depressed splenic function after radiotherapy in the earlier years of this review, when this risk was not appreciated. Other lesions included a mesenchymal tumour of small bowel, a benign osteocartilaginous mesenchymoma of the chest wall, and a haemangioendothelioma of thigh, all of which were successfully treated by resection alone. One patient presented with congenital neurofibromatosis and died of complications of compression by the tumour mass at the level of the thoracic inlet.

HEPATIC TUMOURS

Three patients presented with hepatic tumours, and they illustrate the problems associated with major operation in this group of patients. Two had resection of haemangioendotheliomas, but both died at early postoperative complications. More recently we have operated on a mesenchymal hamartoma (a less vascular lesion) with a successful outcome, and no residual tumour was found on follow-up examination.

TUMOURS OF THE EYE AND ORBIT

Three patients presented with retinoblastomas; two of these were bilateral and both had strong family histories. All three were treated with a combination of operation, radiotherapy, and photocoagulation, and all survived. A benign orbital teratoma was successfully treated by enucleation alone.

SQUAMOUS CARCINOMA

A metastasising squamous carcinoma presenting as a mass over the frontal region at birth. The baby rapidly succumbed without treatment.

Discussion

When analysing the data we must consider the factors that influence both complications and survival. Complications fall into several categories Firstly, the tumour can cause complications by local mechanical restriction of vital functions, or by metastatic disease. Each type of treatment is associated with particular complications. Operations may be complicated by haemorrhage, the necessity for organ resection incompatible with existence, and depression of the immune response. Neonatal tissues have an increased susceptibility to ionising radiation (especially brain, bone, lung, kidney, liver, and spleen) and irradiation can cause depression of the immune response. Neonates are particularly sensitive to cytotoxic drugs, and these also depress the immune response. This series illustrates complications in all the above categories. Campbell *et al*[10] in a review of 102 malignant neonatal tumours also emphasised the difficulties in their management, but confirmed the great potential for cure in this group

Tumour markers are important in the diagnosis and follow up of patients with solid tumours. The biological markers of clinical value include the tumour associated oncofetal antigen, α fetoprotein, which is useful in hepatic tumours (hepatoblastoma), teratomas, and germ cell tumours [11] The products of tumour or host metabolism may also be useful as tumour markers—for example vanillymandelic acid and hydroxymethylmandelic acid, which are produced by 90% of neuroblastomas. Inappropriate hormones may be produced, including vasoactive intestinal peptide in some neural crest tumours, and inactive renin in renal tumours of childhood.[12] Useful enzymes include neurone specific enolase, which is a tumour marker in neural crest tumours. Monoclonal membrane markers are as helpful in diagnosing T and B cell lymphomas as they are in neural crest tumours. Tumour markers will have an increasingly important role in diagnosis and monitoring of response to treatment in this difficult group of patients in the future.

Histological grade is an important indicator of tumour behaviour.[4] Soft tissue sarcomas, renal tumours, and neuroblastomas may be divided into groups with favourable or unfavourable prognoses.[13 14] The description of the mesoblastic nephroma by Bolande *et al* in 1967 revolutionised attitudes towards renal tumours in neonates.[15] It is now thought that half of presumed nephroblastomas in infants under 1 year of age are mesoblastic nephromas.

The importance of this review is to identify factors that could help improve survival rates for neonates who will present with tumours in the future. To achieve this, a knowledge of the natural history of histologically diagnosed tumours is vital. Examples include the excellent results achieved with conservative management of congenital mesoblastic nephromas[10] and stage IVs neuroblastomas.[16] Early operation is often the treatment of choice, and intensive supportive care is essential. The lower mortality seen over recent years (table 1) is probably a reflection of improved facilities for intensive care combined with a better understanding of tumour behaviour and knowing when to take a more aggressive approach. Some neonatal tumours in Glasgow, particularly in the early years of the study, have been missed as methods of record keeping have changed; recent figures are, however, more complete. A neonatal tumour registry would greatly improve documentation of these tumours. The overall survival in this study of 67% indicates that these tumours have great potential for cure and deserve to be treated actively in a coordinated way. An enthusiastically supported neonatal tumour registry would greatly assist dissemination of information on methods of treatment and outcome in these uncommon tumours. A neonatal tumour registry would also allow for surveillance of intellectual development, growth, reproduction, detection of second tumours, and identification of families at risk.

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Technical editor's note

From January 1989 results and measurements in the *Archives of Disease in Childhood* will be given in SI units only. Would contributors please ensure that all results in manuscripts, tables, and figures submitted from now on are in SI units otherwise publication may be delayed. Exceptions to this are:

(a) Blood pressure in mm Hg;
(b) Ventilation pressure in cm H_2O;
(c) Concentration of drugs,
(d) Concentration of any substance where the molecular weight is not known accurately

No old units or conversion factors should be submitted in manuscripts: conversion is the responsibility solely of the author.

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Short reports

Leukoencephalopathy after prophylactic radiation for leukaemia in ataxia telangiectasia

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SUMMARY Children with ataxia telangiectasia have a high probability of developing acute lymphoblastic leukaemia, and have increased sensitivity to chemotherapy and irradiation. We report a 5½ year old boy who had undiagnosed ataxia telangiectasia when he presented with acute lymphoblastic leukaemia. He subsequently developed a chemoradiation induced leukoencephalopathy after conventional central nervous system prophylaxis.

In ataxia telangiectasia there is a high incidence of neoplasia and an increased sensitivity both to radiation and to chemotherapeutic agents. We present a case report of a boy with undiagnosed ataxia telangiectasia who developed an acute leukoencephalopathy after prophylactic cranial irradiation and intrathecal methotrexate for acute lymphoblastic leukaemia.

Case report

A 4½ year old boy initially presented with clumsy gait. His gestation, delivery, and early development were normal. From 2 years his speech was noted to be poorly formed, he dribbled constantly, and his gait was unsteady On examination he had mildly dysarthric speech and his gait was clumsy but there were no signs of ataxia, oculomotor apraxia, nystagmus, or telangiectasia. Muscle tone and power were normal, his reflexes were brisk, but his plantar responses were flexor. A provisional diagnosis of mild cerebral palsy was made.

One year later he represented with acute lymphoblastic leukaemia Treatment following the UKALL VIII 'A' protocol was given. This included prophylactic cranial irradiation of 1800 rads given in 10 fractions and six intrathecal injections of 12 mg of methotrexate. Persistently low white cell counts and anaemia during maintenance treatment led to chemotherapy being withheld for a total of 16 weeks and a dose reduction to 75% of that appropriate for his surface area for the remainder. During this time there began a subacute deterioration in his neurological condition. There was an appreciable deterioration in his higher mental functions. He had choreiform movements of his face and upper limbs, a positive glabellar tap sign, moderate ataxia and dyspraxia of gait, and signs of a spastic tetraparesis. A computed tomogram showed extensive areas of very low attenuation of the white matter in both cerebral hemispheres with several areas of dense calcification.

A full blood count was normal; bone marrow aspiration showed no evidence of a recurrence of the leukaemia. In the cerebrospinal fluid the concentrations of protein and glucose were normal and there were no leukaemic cells. Tests of liver function, and the concentrations of serum copper, caeruloplasmin, and lysosomal enzymes were within normal limits. Early morning plasma cortisol concentrations were low (120 μmol/l; normal range 145–610 μmol/l), however, a tetracosactrin test was normal. Peripheral nerve conduction studies and a nerve biopsy specimen were normal. Viral titres were negative as were cultures of cerebrospinal fluid, blood, and urine. The neurological deterioration continued and a brain biopsy was performed. Histological examination showed features diagnostic of a chemoradiation induced leukoencephalopathy.

In view of these findings a diagnosis of ataxia telangiectasia was considered. A chromosomal analysis showed a generally normal 46 XY karyotype but two cells had a translocation of parts of chromosomes 14 and 15. Cultured blood cells showed an increased sensitivity to radiation when compared with a control, the serum α-fetoprotein concentration was >246 μg/l and the concentration of IgG was 0·65 g/l, IgA was 0·90 g/l, and IgM was

1·07 g/l (all within the normal range); IgE, however, was very low at 0·4 µg/ml. The diagnosis of ataxia telangiectasia was further confirmed when at the age of 8 years conjunctival telangiectasia appeared.

Discussion

Ataxia telangiectasia is an uncommon condition with an estimated frequency of 1/40 000 live births. It is autosomal recessive in inheritance and is characterised by a progressive cerebellar ataxia, dystonia, oculomotor apraxia, oculocutaneous telangiectasia, a predisposition to upper and lower respiratory tract infections, and an increased incidence of malignancy.[1] Ataxia is virtually always the presenting symptom and it typically becomes apparent when the child begins to walk. The ataxia is, however, only slowly progressive and the normal development of motor skills between the ages of 2 and 5 years may mask its progression. In consequence an initial diagnosis of cerebral palsy is often made. The oculocutaneous telangiectasia usually appears later, at between 3 and 6 years. In our patient the presentation was not atypical, although none of the most specific features such as oculomotor apraxia, respiratory tract infections, or telangiectasia were apparent at the age of 4 years.

Children and adults with ataxia telangiectasia are known to be at high risk of developing a malignant neoplasm. The estimated incidence is between 10 and 15% with lymphoreticular neoplasms and acute lymphoblastic leukaemia predominating in patients aged less than 15 years.[2] Chromosomal instability, particularly of chromosome 14, and pronounced chromosomal sensitivity to radiation are accepted hallmarks of ataxia telangiectasia cell lines.[3] The instability of chromosomes and the increased sensitivity to irradiation in ataxia telangiectasia may have important implications not only for the aetiology of the malignancies but also for their treatment. Patients with the disease may have an unexpectedly severe reaction to radiation and to chemotherapy. In children and adults with lymphoma who have been treated with standard radiotherapeutic protocols, it has been reported that severe ulcerative dermatitis and oesophagitis associated with extensive deep tissue necrosis, which sometimes culminates in fatal complications, may occur.[4 5] Acute neurological deterioration after prophylactic cranial irradiation for acute lymphoblastic leukaemia has been reported only once previously.[6] In this paper the outcome of 19 children with ataxia telangiectasia and acute lymphoblastic leukaemia was reviewed; central nervous system prophylaxis was given to five and acute neurological deterioration was reported in three. Of these one child had received cranial irradiation of 1200 rads, the second cranial irradiation of 1800 rads and intrathecal methotrexate, and the third intrathecal methotrexate only. The two children who had central nervous system prophylaxsis but no neurological deterioration died within three months of presentation; it is possible there was insufficient time for neurological deterioration to become apparent. No acute neurological deterioration was noted in the 14 children who did not have central nervous system prophylaxis.

We report this case to highlight both the difficulties of making a diagnosis of ataxia telangiectasia in children aged less than 5 years, and the potentially harmful effects in these children of standard chemotherapy and radiotherapy. Although ataxia telangiectasia is a rare disorder it must be expected to occur with a much higher frequency among children with lymphoreticular neoplasms and acute lymphoblastic leukaemia; it should therefore be considered if the child has a clumsy gait. If ataxia telangiectasia is confirmed the standard therapeutic dose of radiation should be reduced in those with lymphoma, and in children with acute lymphoblastic leukaemia prophylactic cranial irradiation and intrathecal methotrexate should be either withheld or given in reduced dosages.

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Effect of misoprostol on fat malabsorption in cystic fibrosis

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SUMMARY Misoprostol, a synthetic prostaglandin that is known to reduce gastric acid production and stimulate duodenal bicarbonate production, was evaluated in 22 patients with cystic fibrosis. In those patients who had greater than 10% fat malabsorption while taking pancrease the addition of misoprostol significantly reduced the degree of fat malabsorption.

The duodenal intraluminal environment in patients with cystic fibrosis differs from normal in several ways. (1) The concentration of pancreatic enzymes is appreciably reduced, in about 85% of patients, to such low levels that supplemental oral pancreatic enzymes are required to improve absorption of fat, protein, and carbohydrate.[1] (2) Bicarbonate deficiency, resulting also from pancreatic exocrine insufficiency, contributes to a duodenal pH lower than normal.[2] (3) Some patients may also have a hypersecretion of gastric acid.[3] Excessively acidic duodenal pH would be expected to interfere with pancreatic supplement treatment by two separate mechanisms. Firstly, pancreatic enzymes are irreversibly degraded at a low pH—for example, lipase at pH <4.[2] Secondly, most pancreatic enzyme preparations in current use are enteric coated to protect the enzymes against a low pH such as that found in the stomach. The enzymes are not released from these protective coatings, however, until the pH is >5·5. In an excessively acidic duodenum both these factors would lead to a reduction in the amount of enzyme available. Agents which either increase bicarbonate secretion into the duodenum, or decrease gastric acid output, or both, would be expected to increase the amount of active enzyme available in the duodenum. This would be expected to reduce the degree of malabsorption.

Misoprostol is a synthetic prostaglandin of the PGE_2 class that is known to reduce directly gastric acid output and to stimulate bicarbonate secretion from the duodenal mucosa. This study was performed to see if the addition of misoprostol to routine pancreatic supplement treatment would improve absorption of ingested fat.

Patients and methods

Twenty two patients (18 boys, four girls) ranging in age from 1·5 to 10·5 years (mean 4·4) were studied. All patients had been diagnosed as having cystic fibrosis with a sweat chloride concentration >60 mmol/l by pilocarpine iontophoresis. Two patients were withdrawn from the study because of protracted diarrhoea. We report the results of the 20 patients who completed the study.

The study consisted of two 14 day periods. During both periods subjects took their normal dose of pancrease. During one period misoprostol was added (100 μg every six hours). Subjects were randomised to take misoprostol during the first or second period. A three day faecal fat balance study was performed at the end of each 14 day period. Dietary recording was performed for four consecutive days and faecal collection was performed for the last three days of this period. Dietary fat input was calculated using the 'Microdiet' analysis program (Department of Mathematics and Statistics, University of Salford, United Kingdom). Where necessary the program was altered to include Australian foodstuffs

Faecal fat estimation was calculated using the acid titration method of van de Kramer *et al.*[4] The percentage of dietary fat malabsorbed was calculated by the equation:

$$\%\ \text{Fat malabsorbed} = \frac{\text{Three day fat excretion (g)}}{3 \times \text{Mean daily fat intake (g)}}$$

Results

Results for two patients were not calculated because of incomplete dietary recording. Grouped data showed a significant reduction in fat malabsorption. Examination of the results, however, showed that only subjects with >10% malabsorption while taking pancrease (n=13) derived significant benefit from misoprostol. In this group, fat malabsorption fell from an average of 22% while on pancrease to 14% while on pancrease and misoprostol ($p<0·002$) (figure). Pancrease capsule intake did not vary significantly between the two 14 day periods (paired *t* test >0·05). Fat intake between the two study periods was significantly different ($p<0·02$) with the greater input being in the period when misoprostol was administered (77 g compared with 88 g). Six patients reported relief from chronic abdominal pain

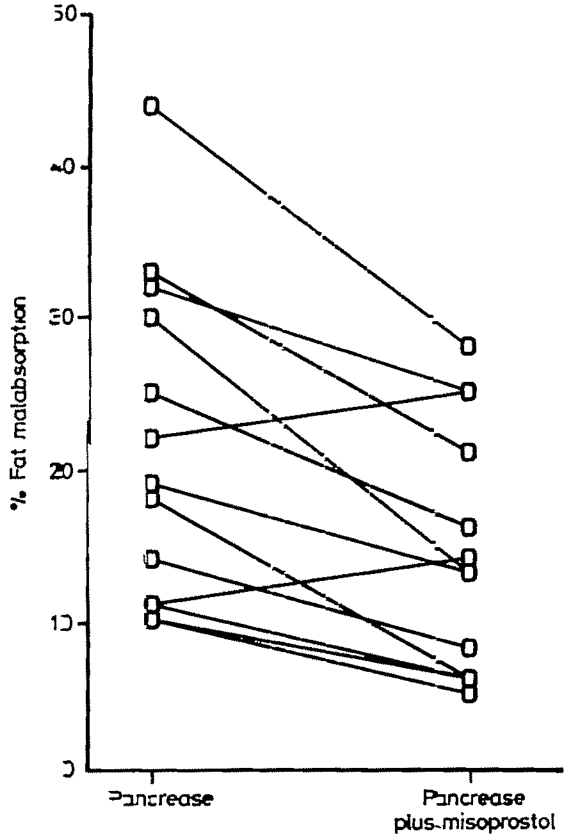

Figure *Comparison of fat malabsorption (as a percentage of ingested fat) in 13 patients taking pancrease and pancrease plus misoprostol.*

while taking the misoprostol. These symptoms returned in five of these patients several days after misoprostol was stopped at the end of the study.

Discussion

The results of the present study have shown that misoprostol can further improve fat absorption in a group of patients with persistent fat malabsorption despite pancreatic supplements. In none of the patients studied, however, did the fat malabsorption return to normal. One possible explanation for this is that the dose of misoprostol was inadequate, there being no recommended paediatric dose of misoprostol currently available. For the purpose of this study the lowest dose effective in reducing acid output in adults was used. It is also possible that this incomplete reversal of the fat malabsorption by misoprostol indicates that other factors in the small bowel are important in fat malabsorption in cystic fibrosis, such as biliary abnormalities and mucosal abnormalities of the small bowel.

Misoprostol is not appreciably absorbed from the gut and produces its actions by a direct effect on the bowel mucosa. Systemic side effects are therefore rare. The only side effects observed in the present study were of a local nature—for example, diarrhoea. The current adult experience of misoprostol has shown that a transient softening of bowel motions is sometimes seen on starting misoprostol (Searle, product information) The two patients who experienced noticeable softening of bowel motions experienced appreciable diarrhoea that did not subside after five days. These patients were withdrawn from the study and their diarrhoea subsided within 48 hours of stopping the misoprostol.

The increased fat input observed during the period of misoprostol administration may well reflect an improvement in appetite in these patients, many of whom suffer decreased appetite due to chronic abdominal pain. The resolution of this pain, as observed in some patients in this present study, may be the explanation for the improved dietary input of fat.

In summary this study has shown that the administration of misoprostol to patients with cystic fibrosis, who have residual fat malabsorption despite taking pancreatic supplements, produces a significant improvement in fat absorption.

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Incidence of retinopathy of prematurity in New Zealand

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SUMMARY The incidence of retinopathy of prematurity has been prospectively assessed in very low birthweight infants born in one year in New Zealand. A total of 26 (11%) surviving infants with birth weight 1000–1499 g had acute retinopathy. Forty one (49%) surviving infants with birth weight 500–999 g had acute retinopathy and of these six (7%) became bilaterally totally blind.

It is clear that the incidence of retinopathy of prematurity has been increasing from the early 1970s, apparently largely as a consequence of enhanced survival of very low birthweight infants (birth weight less than 1500 g) resulting from modern advances in neonatal intensive care.[1] While there have been several reports of the prevalence of retinopathy of prematurity in individual institutions and rather fewer cooperative studies involving several institutions, there have been very few regional or population based studies. In New Zealand there was no information on the annual incidence of acute retinopathy of prematurity or even blindness caused by it. There has, however, been considerable debate as to how far the disorder might be preventable and whether infants suffering from severe retinopathy of prematurity might qualify for compensation from the Accident Compensation Commission.

The aims of the present study were to document all cases of retinopathy of prematurity occurring in very low birthweight infants born in New Zealand in 1986 and to prospectively record data comprising 180 items relating to perinatal and neonatal events. The preliminary results for the national incidence of acute retinopathy of prematurity and early severe visual impairment due to retinopathy of prematurity are reported.

Methods

Considerable planning was undertaken before starting the study on 1 January 1986: this involved discussions with neonatologists and paediatricians in all level III neonatal centres (five) and level II centres (17) in New Zealand. For every infant with a birth weight of less than 1500 g a standard record sheet was completed with details of maternal and birth history and neonatal course. All infants who survived long enough were to have indirect ophthalmoscopy initially at 6 to 9 weeks of age by an ophthalmologist skilled in the technique. The protocol was fully discussed with ophthalmologists in the main centres before the study and a paper on examination technique, with emphasis on the need for adequate mydriasis and scleral indentation, circulated by a senior ophthalmological colleague in Christchurch.[2] Findings at indirect ophthalmoscopy were reported using the International Classification of Retinopathy of Prematurity.[3] If abnormalities were detected at the initial examination the infant was to have further review. If for any reason an infant did not have ophthalmic review at the appropriate time, late review was encouraged

The study received approval from the ethical committee of the Canterbury Hospital Board and the support of the executive of the Paediatric Society of New Zealand.

Results

There were 411 infants with a birth weight 500–1499 g admitted to neonatal units throughout New Zealand in 1986. Seventy four infants died before discharge home giving a survival of 82%

Of 279 liveborn infants with a birth weight 1000–1499 g, 29 died giving a survival to discharge home of 90%. Of 132 liveborn infants with a birth weight 500–999 g, 45 died giving a survival to discharge home of 66%.

Three hundred and thirteen (93%) of the 337 surviving infants with birth weight 500–1499 g had examination by indirect ophthalmoscopy. Two hundred and twenty nine (92%) of the 250 surviving infants with birth weight 1000–1499 g and 84 (97%) of the 87 surviving infants with birth weight 500–999 g were examined.

One hundred and forty one infants (45%) had indirect ophthalmoscopy from six to nine weeks after birth; 88 (62%) of this group had at least two examinations. In 68 infants (22%) a single examination was carried out at 5 weeks of age or earlier but in 24 of these infants this examination was at 35 weeks or more from conception. In 104 infants (33%) the first examination was at 10 weeks of age or more but in 36 of these infants this examination was earlier than 42 weeks' postconception. Thus 201 infants (64%) had an examination at a time most optimal to detect acute retinopathy of prematurity. Additionally in 10% of examinations it was recorded that one or other retina had not been fully seen, usually the extreme temporal periphery.

Sixty seven (21%) infants with birth weight 500–1499 g who had an ophthalmic review had acute retinopathy of prematurity and six (2%) became bilaterally totally blind Twenty six (11%) infants with birth weight 1000–1499 g who had an ophthalmic review had acute retinopathy of prematurity. Forty one (49%) infants with birth weight 500–999 g who had an ophthalmic review had acute retinopathy of prematurity and six (7%) became bilaterally totally blind.

Changes of acute retinopathy of prematurity were observed in 29 (64%) of the 45 infants with gestation of 24–26 weeks, 31 (21%) of the 140 infants with gestation of 27 to 29 weeks, and seven (6%) of the 128 infants with gestation of 30 weeks or more.

Details of the stage of retinopathy of prematurity and gestational age and birth weight are given in tables 1 and 2. Nearly three quarters of the infants with a birth weight less than 1000 g with retinopathy of prematurity had mild stage 1 or 2 disease and only one surviving infant with birth weight 1000–1499 g

Table 1 *Retinopathy of prematurity in very low birthweight infants in New Zealand in 1986 and gestation*

Gestation (weeks)	*No of infants*	*No (%) of survivors*	*No of infants having ophthalmic examination*	*Retinopathy of prematurity stage**				*Total No (%) with retinopathy of prematurity*	*No (%) blind*
				1	*2*	*3*	*4*		
24	9	2 (22)	2	1	1	—	—	2 (100)	—
25	27	16 (59)	16	5	5	—	3	13 (81)	3 (19)
26	43	28 (65)	27	2	6†	4	2	14 (52)	2 (7)
27	47	36 (77)	35	8	3†	1	1	13 (37)	1 (3)
28	63	47 (75)	44	7	2	—†	—	9 (20)	—
29	71	65 (92)	61	3	6	—	—	9 (15)	—
30	60	54 (90)	51	2	0	1	—	3 (6)	—
31	31	30 (97)	28	2	1	—	—	3 (11)	—
32	25	24 (96)	22	1	—	—	—	1 (5)	—
33–3[illegible]	35	35 (100)	27	0	—	—	—	—	—
Total	411	337 (82)	313	31	24	6	6	67 (21)	6 (2)

*If asymmetrical disease was present the stage in the most severely affected eye is shown
†Further case found in infant who died postneonatally

Table 2 *Retinopathy of prematurity in very low birthweight infants in New Zealand in 1986 and birth weight*

Birth weight (g)	*No of infants*	*No (%) of survivors*	*No of infants having ophthalmic examination*	*Retinopathy of prematurity stage**				*Total No (%) with retinopathy of prematurity*
				1	*2*	*3*	*4*	
			Infants weighing 500–999 g					
500–599	3	2 (50)	2	1	1	—	—	2 (100)
600–699	18	10 (56)	10	1	1	—	2	4 (40)
700–799	33	22 (57)	22	4	6	1	—	11 (50)
800–899	35	22 (53)	21	4	4†	2	2	12 (57)
900–999	43	31 (72)	29	4	4	2	2	12 (41)
Total	132	87 (56)	84	14	16	5	6	41 (49)
			Infants weighing 1000–1499 g					
1000–1099	54	44 (81)	42	8	2†	1	—	11 (26)
1100–1199	56	46 (82)	45	6	—	—†	—	6 (13)
1200–1299	43	38 (88)	35	1	2	—	—	3 (9)
1300–1399	60	58 (97)	49	1	3	—	—	4 (8)
1400–1499	66	64 (97)	58	1	1	—	—	2 (3)
Total	279	250 (90)	229	17	8	1	—	26 (11)

*If asymmetrical disease was present the stage in the most severely affected eye is shown
†Further case found in infant who died postneonatally

had proliferative retinopathy of prematurity (stage 3 or more). Only one surviving infant of 28 weeks' gestation or more with retinopathy of prematurity had other than mild stage 1 or 2 disease.

Additionally seven infants who died postneonatally had an ophthalmic review, and three had acute retinopathy of prematurity.

Discussion

Several authors have emphasised the need for population based studies of the incidence of retinopathy of prematurity as a preliminary to a better understanding of the aetiology, prevention, and treatment of this disorder.[1 4] Good prospective follow up of children who have required intensive care is, or should be, an integral part of a newborn intensive care service. Parents and care givers need to know about problems and potential handicaps at an early stage. Knowledge of the incidence of a disorder such as retinopathy of prematurity and whether it is increasing or not, not only facilitates critical review of standards of care but also means that there can be national planning for the future care of children with severe visual handicaps.

Flynn and others have highlighted the fact, also apparent from earlier literature, that if retinal examination is too soon after birth acute retinopathy of prematurity may be missed as changes often develop later in more premature infants.[5] Equally if the examination is too late any acute changes may have regressed and no sequelae be detected. This may account for the wide variation in the reported incidence of acute retinopathy of prematurity.[1]

The main reasons for one third of the infants not having an ophthalmic review at a time most optimal to detect acute retinopathy of prematurity in the present study were that the smallest infants were often too sick for examination to be attempted; that more mature infants were either examined early before transfer to a smaller centre nearer home or had to return to the main centre for examination at a later date; and lastly that some infants failed to attend repeat appointments. Together with the fact that in 10% of examinations the retina, albeit usually the extreme temporal periphery, could not be fully visualised, these factors may contribute to the relatively low incidence of acute retinopathy of prematurity seen in this study compared with some unit based studies in which repeat examinations were carried out until full vascularisation of the retina.[5] On the other hand the proportion of more mature, growth retarded infants in this population based study is likely to be greater than in studies from specialised referral units.

All six infants with stage 4 retinopathy of prematurity were considered to have developed bilateral complete retinal detachments at an early stage even though cicatricial disease is often asymmetrical[5] Data on other sequelae including less severe cicatricial disease are still being collated. The incidence of blindness of early onset from retinopathy of prematurity in surviving New Zealand infants with a birth weight 500–999 g was thus 7%. This figure is similar to the 8% used by Phelps to produce her estimates of vision loss due to retinopathy of prematurity in the United States,[1] and it is also very similar to the 7% who were found to have Kingham grade 3 or 4 retinopathy (severe cicatricial disease and blindness) in the one population based study of the incidence of retinopathy of prematurity in infants with birth weight 501 to 1000 g from the McMaster health region 1977–80.[6]

Details of neonatal care, including vitamin E usage, varied considerably between the different units throughout the country and analysis of the various risk factors for retinopathy of prematurity will be reported subsequently.

The present study is continuing for a second year and it will be important to see if the same pattern of retinopathy of prematurity with respect to birth weight and gestation is repeated. It may be that routine examination should be confined to infants of 30 weeks' gestation or less and less than 1250 g birth weight. To do so would have reduced the number of initial ophthalmic examinations by 34% without missing any proliferative retinopathy.

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Streptokinase for aortic thrombosis

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SUMMARY A neonate developed complete thrombosis of the abdominal aorta after catheterisation of the umbilical artery. This was successfully treated with an intravenous infusion of streptokinase.

Aortic thrombosis is a rare but well recognised complication of catheterisation of the umbilical artery[1] for which the accepted management is surgical thrombectomy.[2] We describe a child who was successfully treated with intravenous streptokinase.

Case report

A baby boy was born at 40 weeks' gestation He weighed 2340 g and was small for gestational age His mother had smoked during the pregnancy. At birth his haemoglobin concentration was 259 g/l and the packed cell volume was 0·75 His blood glucose concentration subsequently dropped to <1·0 mmol/l and he developed respiratory distress for which he required artificial ventilation. An umbilical artery catheter (Argyle size 5F. Sherwood Medical) was inserted and the tip positioned at the level of the body of the 11th thoracic vertebra A dilutional plasma exchange transfusion was carried out and the haemoglobin concentration fell to 225 g/l with a packed cell volume of 0·65. Seventy hours after its insertion the catheter had occluded and so it was removed. Twenty four hours later both the baby's legs were cold and mottled, with no pulses.

An aortogram was performed by the Seldinger technique through the right femoral artery; this showed that the abdominal aorta was completely occluded distal to the origin of the renal arteries (figure).

An intravenous bolus of 1000 U/kg of streptokinase was given, followed by an infusion of 1000 U/kg/hour into a vein on the dorsum of the hand Eight hours later both the femoral pulses were present on Doppler examination. After 30 hours his lower limb pulses were normal and the blood pressure in the right arm was 87/54 mm Hg and in the left leg 84/43. The streptokinase was discontinued and 25 U/kg/hour of heparin given for 48 hours.

Four months later all the pulses were normal and

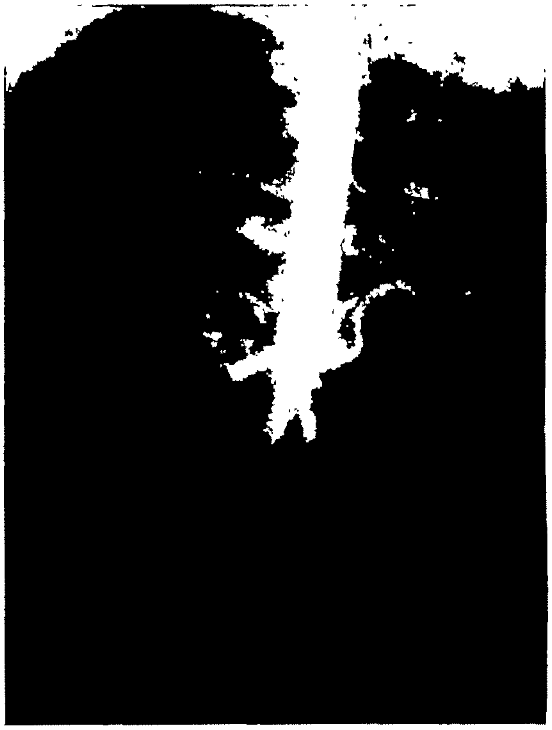

Figure *Abdominal aortogram showing total occlusion of abdominal aorta below origin of renal arteries* the blood pressure in the right arm was 97/58 mmHg, in the right leg 95/55, and in the left leg 100/60. A radionuclide angiogram using ^{99m}technetium showed equal perfusion of both legs

Discussion

Thrombosis of the abdominal aorta is a rare complication of catheterisation of the umbilical artery.[1] Untreated it is usually fatal, and surgical thrombectomy is the accepted management [2 3] The operation is, however, associated with appreciable operative mortality and morbidity, and thrombosis may recur.[4]

In this case an aortogram was performed to confirm the aortic thrombosis. The absence of femoral artery pulsation made the landmarks for percutaneous puncture of the femoral vein difficult. Though there might be concern about passing the catheter through the thrombus and possibly dislodging it, extensive experience of coronary angioplasty in adults with recently occluded coronary arteries has not confirmed this.

Streptokinase is a recognised alternative to thrombectomy in children with arterial thrombosis[5] and we have used it successfully. Haemorrhage from the arterial puncture site is the main complication, but the incidence may be reduced by careful management. We recommend that streptokinase should only be given if the fibrinogen concentration is greater than 1·5 g/l, and that this should be checked after two hours, and subsequently at four hourly intervals. If the fibrinogen concentration falls below 1·0 g/l the infusion should be stopped and heparin given.[6] When the fibrinogen concentration rises above 1·0 g/l the streptokinase infusion may be restarted. We have found a decrease in the fibrinogen concentration is usually associated with successful thrombolysis.

This case shows the value of streptokinase as an alternative to operation in the management of aortic thrombosis following catheterisation of the umbilical artery.

We thank Dr PJ Todd for permission to report this case

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Acute transient myositis due to Toxocara

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SUMMARY Two children presented with spontaneous, isolated swelling of the lower half of the left leg; this was diagnosed as acute myositis of unknown aetiology. Further investigations showed antibodies to Toxocara. The symptoms resolved within 72 hours and the children were discharged on no treatment.

The genus Toxocara comprises parasitic helminths that are capable of causing either asymptomatic or symptomatic infection in humans. The two common manifestations of infection are visceral larva migrans and ocular larva migrans. Organs affected in the former category include the liver, lungs, brain, and heart. We describe two children in whom infection presented as acute myositis. To our knowledge this association has not been described previously.

Case reports

Two children, a girl aged 1½ and a boy aged 2½, both local children, presented to our department within a six month period. In each case the parents had noticed the spontaneous onset of isolated swelling of the lower half of the left leg. The children were otherwise asymptomatic

Examination showed diffuse, non-tender, firm swelling of the muscle bulk posterior to the length of the left tibia and fibula. There were no associated overlying skin changes. Initial investigation was by radiography of the left tibia and fibula and blood was taken for a full blood count and erythrocyte sedimentation rate. The results are shown in the table.

Both children were diagnosed as having acute myositis of unknown aetiology They were discharged home and reviewed a week later In both cases the symptoms had resolved within 72 hours of the initial presentation. Both remained completely asymptomatic thereafter

Further investigations were performed to find the cause of the eosinophilia. The boy had antibodies to Toxocara alone while the girl showed evidence of infection by both Toxocara and *Trichinella spiralis* (table). We believe, however, that the similarity of the symptoms in both children, the transient nature of the myositis, the absence of circumorbital oedema and the high titres of Toxocara antibody indicating active infection, combine to favour a diagnosis of toxocariasis rather than *Trichinella spiralis* infection in her case.

As both children were diagnosed as having toxocariasis they had formal ophthalmic examinations, which were normal. They required no specific treatment and were discharged to the care of their family doctor.

Table *Results of investigations performed on two patients with myositis*

	Girl	*Boy*
Radiography of tibia/fibula	Normal	Normal
Full blood count:		
Haemoglobin (g/l)	109	125
White cell count ($\times 10^9$/l)	16·0	15·0
Neutrophils (%)	15	39
Lymphocytes (%)	50	22
Eosinophils (%)	30	35
Erythrocytes sedimentation rate (mm in the first hour)	20	12
Trichinella spiralis antibody titre	1/128	Nil
Toxocara antibodies (ELISA)*		
Acute	1 12	1·01
Convalescent	0 45	1 5

*An ELISA score of 0·7 indicates active infection

The actual source of infection remained undetermined in either case.

Discussion

Although the parasite Toxocara was originally identified in 1782, it was not until 1952 that infection of humans was first documented.[1] Its prevalence in the population is uncertain but one study showed that 2% of apparently healthy people are infected with Toxocara.[2] Infection is clinically manifest as visceral larva migrans or ocular larva migrans. There are important clinical and epidemiological differences between the two entities. The former presents in children less than 4 years of age, usually with an associated history of pica. Minor symptoms of malaise, fever, and cough in the presence of hepatomegaly and appreciable eosinophilia are usual. However, more serious morbidity has been described when the myocardium[3] and central nervous system[4] are affected.

Ocular larva migrans typically occurs in adults in the absence of evidence of visceral larva migrans and no associated eosinophilia. It is possible that the immune response occurring in chronically infected children protects them against ocular disease.

The diagnosis of toxocariasis should be considered in a child whose white cell count shows appreciable eosinophilia. Currently the best method of making a laboratory diagnosis is the enzyme linked immunosorbent assay (ELISA). It has a sensitivity of about 80% and a specificity of 90%.[5]

Neither of the children reported was offered treatment. Controversy exists over the effectiveness of antihelminthic drugs to relieve symptoms and eradicate infections. As the natural course of the disease seems to be self limiting most workers elect to treat only severe or life threatening infections.

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Pneumococcal arthritis mimicking juvenile chronic arthritis

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SUMMARY Two young children referred as pauciarticular juvenile chronic arthritis were subsequently found to have pneumococcal septic arthritis.

Failure to diagnose septic arthritis can lead to serious joint damage, but it may not be easy to exclude. Morrisey and Shore, recorded 10 out of 32 cases of septic arthritis wrongly diagnosed in the first instance.[1] We report two children whose initial investigations for septic arthritis were negative, but who had persistent symptoms and had been diagnosed as juvenile chronic arthritis.

Case reports

The children, both boys, aged 20 months and 3 years, were referred for management of pauciarticular juvenile chronic arthritis. Both gave a three to four week history of swelling of one knee with refusal to bear weight; one child also had transient swelling of an ankle. A five day course of oral antibiotics for a sore throat had been given to the older child before the onset of the knee problem. The younger child had had pneumococcal pneumonia six months earlier. Both children had had several sets of negative blood cultures at the referring hospitals and were being managed with non-steroidal anti-inflammatory drugs.

On presentation both children had an acutely tender hot swollen knee joint that was held firmly in flexion. Although refusing to move the joint neither child was acutely toxic or ill. One developed a spike of fever and more pain on stopping the non-steroidal drug. Both children were anaemic, with haemoglobin concentrations of 75 and 96 g/l, white cell counts were normal, but the erythrocyte sedimentation rates in the first hour were 100 and 95 mm. Aspiration of the joints showed turbid fluid with a high polymorph count. This fluid grew *Streptococcus pneumoniae* (sensitive to benzylpenicillin) in one child. The other boy, who had received antibiotics before admission, had sterile joint fluid, but a blood culture taken at the same time as joint aspiration yielded the organism. Both children were managed with six weeks of benzylpenicillin and appropriate physiotherapy and splinting and made a complete recovery. Further immunological investigation of the child with previous pneumococcal infection gave normal results.

Discussion

Both these children had had a swollen joint for four weeks. The striking clinical feature was the exquisitely tender joint and its immobility. Basic investigations showing a very high erythrocyte sedimentation rate and a low haemoglobin concentration are unlikely in pauciarticular juvenile chronic arthritis. The state of the joint and these laboratory features were indications for aspiration of the joint.

Antibiotics, however briefly administered, affect the growth of organisms from blood and joint fluid, and repeated cultures should be taken if a joint remains hot and tender. Despite repeated attempts, up to 40% of synovial fluid cultures are uninformative[2] and here culture of blood or other site of local infection may help.

Failure to grow the organism from the joint in one child raises the question of whether the arthritis was 'reactive' in this patient. Reactive arthritis has been reported after pneumococcal meningitis,[3] although is much more commonly described after haemophilus and meningococcal infections. The mechanism is presumed to be an immunological one with an inflammatory response to bacterial cell wall products rather than live organisms in the joint.[2] Cases of reactive arthritis after bacterial sepsis that were reported by Rush *et al* did not respond to antibiotics,[4] whereas our patient responded dramatically to benzylpenicillin. Taking this clinical response with the positive blood culture at the time of joint aspiration, we feel justified in also calling this case septic arthritis.

In one child the presence of another swollen joint was misleading, but transient synovitis occurs in more than one joint in up to 10% of cases of septic arthritis or osteomyelitis. Non-steroidal drugs were effective in suppressing constitutional signs of sepsis in one child and thus tended to mask the clinical picture of septic arthritis.

We thank Drs AM Mobarak and B Taylor for permission to report their patients, and Mr CM McCullough who performed the joint aspirations

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Growth hormone, suspected gonadotrophin deficiency, and ring 18 chromosome

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SUMMARY A boy with a ring 18 chromosome karyotype was referred because of short stature; he had growth hormone deficiency and possible hypogonadotrophic hypogonadism. Many children with major chromosomal abnormalities are short, but this case emphasises the need to consider growth hormone deficiency in addition.

About 60 patients with a ring 18 chromosome karyotype have been reported. Phenotypically they are short and obese with mild dysmorphic features including hypertelorism, epicanthic folds, slight micrognathia, and small hands with short, tapering fingers. Boys may have a small penis and cryptorchism. All have pronounced retardation of growth and there have been two reports of additional growth hormone deficiency.[2] [3] We report a child with growth hormone deficiency and possible gonadotrophin deficiency.

Case report

The boy was born to healthy non-consanguinous parents at 40 weeks' gestation weighing 2900 g. He had a low Apgar score and resuscitation included a brief period of intubation. His development was delayed and at 3·5 years he was noted to be short (height −3 SD) and comparatively obese (weight 10th centile) with an unusual facies. Examination of the peripheral lymphocytes showed an abnormal male karyotype of 46 chromosomes, including one ring 18 chromosome. The precise breakpoints in the formation of the ring chromosome could not be determined, but the morphology and stability of the ring implied that the deleted distal segments were comparatively small. The parents' chromosomes were normal.

At the age of 12 he was referred to the growth clinic because of pronounced retardation of growth and obesity. His height was 112 cm (−4·8 SD), and he weighed 37 kg (50th centile). He had several of the dysmorphic features that are described in children with ring 18 karyotype including a small penis (<2 cm long) with small soft testicles (<2 ml volume) (figure). His sense of smell was normal, and his skeletal age was 9·1 years. Serum thyroxine, thyroid stimulating hormone, prolactin, and cortisol concentrations were all normal. A sequential insulin and arginine stimulation test after priming with 100 µg ethinyloestradiol daily for three days confirmed growth hormone deficiency with unrecordable growth hormone concentrations despite adequate hypoglycaemia (4·2 mmol/l→2 mmol/l). The pituitary sella was small but a brain scan was normal. He was given growth hormone (Somatonorm) 4 units subcutaneously three times a week, and his height velocity (which had been 4·8 cm/year before treatment) increased to 10·8 cm/year during the first full year of treatment.

At the age of 14·3 years he was still prepubertal. His gonadotrophin response to gonadotrophin releasing hormone was poor with a peak measurement of luteinising hormone of 3·1 IU/l and a peak measurement of follicle stimulating hormone of 2·1 IU/l. Basal testosterone concentration was 0·1 nmol/l. The addition of testosterone enanthate 100 mg intramuscularly monthly has accelerated his growth (which at the time of writing was 9·7 cm/year), and induced sexual maturation.

Discussion

A ring 18 chromosome karyotype is comparatively rare; there is loss of small distal segments of both long and short arms of the chromosome so that a mixture of physical signs characteristic of 18p− and

18q− can be expected[4] Transmission of the disorder from parent to child has been reported[5] but most cases are mutations.

We know of two reports of children with chromosome 18 deletions and growth hormone deficiency,[2 3] but most authors do not measure growth hormone concentrations. There are reports of primary hypoparathyroidism and primary hypothyroidism, but none of gonadotrophin deficiency though some boys have small penises and testicles.

A causal association between growth hormone deficiency and 18 chromosome deletion is difficult to justify, as the gene for growth hormone production seems to lie on chromosome 17. Our patient was resuscitated in the neonatal period and perinatal asphyxia causing hypothalamic damage cannot be ruled out as the cause. His brain scan was normal so that there was no gross anatomical cerebral abnormality, but the pituitary sella was abnormally small.

Three reports of growth hormone deficiency in a comparatively rare chromosome disorder suggest that hypopituitarism should be sought for in children with this chromosome deletion and short stature. Some children seen in growth clinics are dysmorphic, or have minor or major chromosome abnormalities, and usually paediatricians regard these children's short stature as part of their particular disorder. This case emphasises the need to measure growth hormone concentrations if height velocity is decreasing or retardation of growth is severe.

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Glaucoma as an early complication of Hurler's disease

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SUMMARY We report three cases of Hurler's disease in which glaucoma developed in early childhood. We draw attention to the fact that glaucoma may be a commonly unrecognised early complication of this condition.

Glaucoma has been reported as a complication of mucopolysaccharide (MPS) storage diseases in adults with milder variants, such as Scheie disease (MPS IS).[1] A single case of glaucoma in a child with Hurler's disease (MPS IH) was reported by Spellacy *et al.*[2] The authors speculated that glaucoma only develops late in milder forms of MPS storage diseases, and is rarely seen in patients with MPS IH because of their short life expectancy.

Case reports

CASE 1

A girl, weighing 3886 g, was born at term to nonconsanguinous black parents. Noisy breathing and snoring were reported from early infancy. There was initially mild, but subsequently more severe and progressive, developmental delay. Congenital glaucoma was suspected at 16 months of age because of corneal clouding. At 18 months of age, she had many characteristic clinical features of MPS storage, including large head (49·0 cm, >98th percentile), depressed nasal bridge, thick lips, large tongue, dysplastic teeth, hepatosplenomegaly, and a mild gibbus and flaring of the lower ribcage. Radiographic examination of the skeleton showed changes typical of Hurler's disease (MPS IH). The diagnosis was confirmed by the demonstration of absence of α iduronidase in leucocytes and cultured skin fibroblasts.

Pronounced corneal opacities were noted on examination. Examination under anaesthesia showed corneal diameters of 12·25 mm in the left eye and 12·50 mm in the right eye. Pressure was 3·07 kPa in the right eye, and 3·20 kPa in the left. There was central cupping of optic disks with cup/disk ratio of 0·4 in both eyes. The cups were vertically elongated. A right and left goniotomy was performed, and pilocarpine 4% and chloramphenicol/hydrocortisone/polymyxin B ointment were instilled. The postoperative course was uneventful.

CASE 2

A boy, born prematurely at 37 weeks' gestation weighing 2000 g, had his neonatal course complicated by the development of hyaline membrane disease, which progressed to bronchopulmonary dysplasia. He had recurrent colds and otitis media throughout infancy. Bilateral inguinal hernia repairs were required twice because of recurrence. Developmental milestones lagged behind the normal. At 16 months of age he developed persistent tearing and photophobia in both eyes. At 18 months a diagnosis of congenital glaucoma was made. On examination, bilateral corneal opacities and the characteristic clinical features of Hurler's disease were noted. The diagnosis of MPS I was confirmed by the demonstration of deficiency of α iduronidase in peripheral blood leucocytes.

On examination under anaesthesia corneal diameters were 12·75 mm in the right eye and 12·00 mm in the left eye. Both corneas were extremely cloudy, making ophthalmoscopy very difficult, especially in the left eye. Optic disks were pale with a cup/disk ratio of about 0·6–0·7. The intraocular pressures were 1·60 kPa in the left and 3·07 kPa in the right eye. With the aid of a Barkan lens, bilateral goniotomies were performed without difficulty. Pilocarpine 4% and chloramphenicol/hydrocortisone/polymyxin B ointment were instilled into both eyes; the postoperative course was uneventful.

CASE 3

A girl was born at term and developed normally until the age of 5 months. She was referred at the age of 7 months by her family physician for investigation of recurrent upper respiratory infections, macrocephaly, hepatosplenomegaly, and recent developmental delay. On examination, she was 69 cm in height (90th percentile), weighed 8·48 kg (75th percentile); head circumference was 50 cm (>98th percentile). The typical facial appearance and other clinical features of Hurler's disease were noted. The diagnosis of MPS I was confirmed by the demonstration of absent α iduronidase activity in peripheral blood leucocytes.

Examination under anaesthesia at the age of 17 months showed corneal diameters of 12·25 mm bilaterally and normal fundi. There was no evidence of papilledema or increased intraocular pressures. Slight corneal opacities were noted bilaterally. At 5 years of age, she again underwent examination under anaesthesia because of decrease in visual acuity. By that time corneal opacities had increased appreciably; however, the details of the irides could still be discerned. Corneal diameters were 12·5 mm bilaterally. The intraocular pressures measured 3·73 kPa in the right and 4·00 kPa in the left eye by applanometer tonometry. Diagnosis of glaucoma was made, and treatment with pilocarpine drops was started.

Discussion

Glaucoma is a well recognised, but apparently rare, complication of MPS storage diseases; as a presenting problem it is virtually unknown. In two of the three cases reported here, however, the diagnosis of a storage disorder had not been made when glaucoma developed before the age of 5 years. The eye complaints were typical: excessive tearing, photophobia, and clouding of the corneas (table). Although characteristic also of glaucoma, the clouding of the corneas in these cases was attributable primarily to MPS storage. The diagnosis of glaucoma was supported by the demonstration of increased corneal diameters, cup/disk ratios greater than 0·3, and the presence of increased intraorbital pressures (table). In one case the patient improved with medical treatment alone; in the other two goniotomies were performed.

Table *Ocular findings in patients*

Case No	*Presenting symptoms*	*Eye*	*Corneal diameters (mm)*	*Intraocular pressure (kPa)*	*Disk/cup ratio*
1	Corneal opacities	Right	12·50	3·07	0·4
		Left	12·25	3·20	0·4
2	Redness of the eye	Right	12·75	3·07	0·6–0·7
	Photophobia, excessive tearing	Left	12·00	1·60	0·6–0·7
3	Decrease in visual acuity	Right	12·50	3·73	Not examined
		Left	12·50	4·00	

The most common cause of infantile glaucoma is interference with aqueous outflow caused by arrest of the development of the trabecular meshwork of the anterior chamber angle. In MPS storage diseases, the trabecular meshwork becomes engorged and distorted by accumulating MPS, which also causes thickening of the extracellular matrix in sclera and corneas, resulting in further constriction of the anterior chambers.[3] [4] Distortion of the meshwork in the corneoscleral junction and adjacent to the canal of Schlemm interferes with the flow of aqueous humour through the endothelial lining.[5] The presence of incompletely degraded MPS in the outflow apparatus is also thought to inhibit hyaluronidase and other degradative enzymes involved in the maintenance of normal aqueous outflow.[6]

Glaucoma may be a more common early complication of Hurler's disease than has been previously appreciated. The recognition of the complication is undoubtedly obscured by the fact that one of the principal clinical features of glaucoma in infants—corneal clouding—is also a prominent finding in Hurler's disease. Corneal opacification in infantile glaucoma is due to aqueous entering corneal stroma via microscopic breaks in Descemet's membrane resulting from increased intraocular pressure. The separations are permanent and appear as wavy parallel lines—usually curvilinear and horizontal, on the inner side of the cornea. In Hurler's syndrome the avascular noninflammatory corneal clouding is a result of lysosomal engorgement with MPS material. Here, fine grey punctate opacities are first seen in the anterior stroma, then in the posterior stroma and endothelium. Clinically, however, these two types of corneal clouding are undistinguishable. Early recognition and treatment of the glaucoma would not be expected to contribute appreciably to the longevity of children with Hurler's disease; however, it clearly enhances the quality of life of affected patients. Physicians attending patients with MPS disorders should be alert to the possibility of the problem occurring, and obtain appropriate ophthalmological consultation should ocular complaints possibly attributable to glaucoma develop.

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British Paediatric Association

Annual meetings

At York University:
1989 April 11–14

At University of Warwick:
1990 April 3–6
1991 April 16–19
1992 April 7–10
1993 April 20–23 (provisional)
1994 April 12–15 (provisional)

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Special report

Paediatric manpower: towards the 21st century

W J APPLEYARD AND A D M JACKSON

British Paediatric Association

SUMMARY The British Paediatric Association (BPA) has carried out a national survey of paediatric medical manpower in the hospital and community child health services. The results of the survey relating to England and Wales are presented and compared with Department of Health and Social Security (DHSS) manpower statistics. On the basis of the survey findings and current trends in the pattern of paediatric care paediatric manpower requirements over the next 10 years are estimated.

The consultative document, *Hospital Medical Staffing: Achieving a Balance* sets out three basic objectives[1]: (1) to increase the number of consultants; (2) to match more closely the number of doctors in training to expected consultant opportunities; and (3) to ensure the necessary support for consultants to provide 24 hour cover in the acute specialties Detailed plans for the implementation of these proposals were drawn up by a steering group on behalf of the United Kingdom Health Departments, the Joint Consultants Committee, and the Chairmen of Regional Health Authorities and published in their report, *Plan for Action*[2] In preparation for these impending changes in staffing structure the BPA has undertaken an extensive survey of present manpower in paediatrics and has reviewed manpower needs in the specialty over the next 10 years.

Three important trends in paediatrics must be taken into account when future manpower needs are being considered: (1) the integration of the hospital and community child health services within districts, (2) the growth of the paediatric specialties and (3) the continuing developments in general and neonatal paediatrics in district general hospitals.

(1) Integration of district child health services

The Committee on Child Health Services—the 'Court Committee'—recommended that the district child health services should be integrated, with a two tier system based on comprehensive primary care firmly linked with supporting consultant and hospital care.[3] After protracted discussions there is now broad agreement between the government and the profession that this recommendation should be implemented.

The Child Health Forum was set up in 1985 by the British Medical Association (BMA) and consisted of representatives from community medicine, community health, general practice, hospital consultants, and hospital junior staff. Its report[4] has been accepted by all the 'craft' committees, the Council and the Annual Representatives' Meeting of the BMA, and by the Joint Consultants Committee. The Forum envisages in every health district a consultant led service providing secondary child health care with the necessary supporting services provided partly by doctors in training and partly by doctors in a service career grade with delegated responsibility from the consultants Initially the secondary child health service will require a minimum of one consultant paediatrician in community child health (CPCCH) for each district, accepting that there will be a subsequent expansion in numbers in accordance with local needs. CPCCHs will have to be supported by the necessary specialist training posts, incumbents of which may rotate between hospital and community child health. As the necessary transition from senior clinical medical officer to CPCCH proceeds it is important that the specialist responsibilities in community child health at present undertaken by senior clinical medical officers be fully covered in each health district and current provision suggests the need for about 2·5 CPCCHs per district.

(2) The growth of the paediatric specialties

When the Court Committee published its report in 1976 there were 70 consultants working as paediatric specialists in the United Kingdom and the committee recommended an increase to 137.[3] In the 10 years since then growth in the paediatric specialties has been far more rapid than was foreseen. A survey carried out by the specialty groups of the BPA in 1986 identified 247 consultant paediatricians practising part time or whole time in a specialty within paediatrics in the United Kingdom (table 1) and this total is an underestimate as there was only an 80% response to the inquiry

Official statistics for the number of consultant paediatricians in specialties other than paediatric neurology are not available. There is some uncertainty about how most of these specialist paediatricians are classified but paediatric cardiologists are known to be recorded as adult cardiologists in the DHSS manpower tables.

The present need for further growth in the paediatric specialties in England and Wales is estimated by the BPA specialist groups to amount to some 390 posts. Most of these posts will of necessity be based in university hospitals and the numbers required take account of the need both for research and for tertiary patient care.

(3) Developments in general and neonatal paediatrics in district general hospitals

Information on the workload of consultants in the National Health Service (NHS) was recorded in the Office of Health Economics survey published in the 1978 Doctors' and Dentists' Review Body Report.[5] Consultant general paediatricians had the highest recall rate to hospital and a significant number of them were on call on a one in two rota throughout their professional careers. Since then the intensity of paediatric care in both general and neonatal wards has increased and it is now only possible to provide a satisfactory level of 24 hour consultant cover if consultant general paediatricians work a minimum on call rota of one in three. This entails at least three consultant general paediatricians per district with four or perhaps more in larger districts.

Table 1 *Numbers of consultants in the paediatric specialties in the United Kingdom (BPA 1986)*

Specialty	*No*
Endocrinology	21
Gastroenterology	26
Metabolic disease	17
Nephrology	24
Neurology	30
Oncology/haematology	38
Perinatology	66
Respiratory disease	25
Total	247

Bearing these trends in mind the BPA foresees consultant paediatric manpower for England and Wales rising to a total of 1490 over the next 10 years or so This total can be broken down as follows: to provide 2·5 CPCCH per district, 500; to provide the estimated number of paediatric specialists, 390; and to provide at least three general paediatricians per district, 600.

The BPA survey

In the summer of 1986 questionnaires were sent to a named consultant paediatrician in every health district, health board, and postgraduate hospital with paediatric staff in the United Kingdom. In order to ensure that the manpower data were as accurate and up to date as possible it was considered essential to obtain the necessary information directly from a professional source within the district rather than from administrative records. Information was requested on the numbers and sessional commitments of all medical paediatric staff, including honorary staff, in both hospital and community child health services. The dates of retirement of senior staff were also requested and for all but senior house officers and clinical medical officers names were requested to avoid duplication. Where the consultant paediatrician was unable to provide details of community child health staff he or she was asked to enlist the aid of a senior member of that staff. Respondents were invited to indicate their estimate of the need for additional consultant staff in the district over the next 10 years.

The work entailed in completing these questionnaires was considerable and posed problems for the respondents, particularly those in postgraduate hospitals or in districts with university hospitals. Delays in returning questionnaires were therefore inevitable but by the autumn of 1987 complete data had been received from every hospital and community child health service in the United Kingdom The data have been recorded on computer discs in table form giving numbers of staff and whole time equivalents in hospital and community by district and region. This is now the definitive record of paediatric manpower in the country in 1986 and the BPA intends to update the figures regularly. A start has already been made on collecting revised data for 1988.

In view of the separate arrangements for manpower in Scotland and Northern Ireland the data and discussions in the remainder of this paper refer to paediatric manpower in England and Wales only. Table 2 summarises the main findings of the BPA survey and shows the equivalent DHSS figures (paediatrics and paediatric neurology) for comparison.

Consultants

The BPA survey records 744 consultant paediatricians (642 whole time equivalents) of whom 115 hold honorary appointments with the NHS. The comparable DHSS figure for 1986 is only 645 (583 whole time equivalents).[6] The BPA data however, are supported by the names of individual consultants and must be considered more accurate. The disparity is perhaps explained in part by the extent to which consultant paediatricians in the specialties apart from paediatric neurology are recorded within the adult specialty and in part by the number of CPCCHs who may be recorded in community medicine tables. These differences underline the need for meticulous collection of manpower figures from local sources.

In the BPA survey consultants with five or more sessions in community child health numbered 47 and they held appointments in 35 health districts. Some 20 new CPCCH appointments were made in 1987 so it is likely that about 145 of the 200 districts in England and Wales have not yet made a CPCCH appointment. The survey identified 792 senior clinical medical officers (572 whole time equivalents) working in child health, a little over 2·5 whole time equivalents per district, which is the BPA recommended district establishment for CPCCH. As there were 640 senior clinical medical officers above the age of 50 in 1986[7] there will clearly be ample opportunities for reaching the desired level of 2·5 CPCCH per district over the next 10 years by replacing retiring senior clinical medical officers without the need for new money, at least for the first few years of each appointment.

Table 2 *Paediatric manpower in England and Wales in 1986*

Grade	*BPA survey*		*DHSS*	
	No	*Whole time equivalents**	*No*	*Whole time equivalents**
Consultant	744	642	645	583
Senior registrar	200	—	159	—
Registrar	356	—	287	—
Senior house officer	1080	—	1031	—
Associate specialist	40	24	28	21
Hospital practitioner	36	7	24	5·6
Clinical assistant	184	38	187	40
Senior clinical medical officer in child health	792	572	Not recorded	

*Whole time equivalents for hospital staff were calculated, as in the DHSS hospital medical staff tables, by dividing the number of weekly sessions by 11 The same calculation was used for community medical staff rather than the method of dividing the weekly number of hours by 37 used in the DHSS community medicine and community health service medical staff tables

Senior registrars

Table 3 shows the number of senior registrar posts and their type, as identified in the BPA survey. The difference between the BPA figure of 200 and the 159 recorded by the DHSS[6] has been almost completely resolved by further inquiries to regions by the DHSS, which have raised the official total to 194 and have shown a further three paediatric senior registrar posts recorded as posts in adult cardiology.

Assuming an average duration of four years for senior registrar posts and an average of 30 years for the professional life of a consultant the required ratio of senior registrars to consultants is 1:7. When the specialty is ultimately in a steady state with 1490 consultants, the number of senior registrar posts needed will therefore be roughly 210. During the period of growth in the number of CPCCH posts over the next 10 years, however, there will be a need for a temporary increase in the number of senior registrars in the field of community child health. The overall total of senior registrar posts required can be calculated from the expected number of consultant vacancies. We estimate the number of consultant retirements and losses to be 22 per year, the number of retiring senior clinical medical officers who will be replaced by CPCCH to be an additional 30 per year, and growth in the other fields of paediatrics to continue as in the last few years—that is, at a rate of 20 per year. This gives a total of 72 consultant posts a year which must be supplied by 288 (72×4) senior registrar training posts. Any retirements of senior clinical medical officers in excess of 30 will provide

Table 3 *Numbers of senior registrars. BPA survey in England and Wales in 1986*

Type of post	*No*
NHS full time	87
NHS part time	21
Honorary (university)	52
Honorary (soft money)	31
Research	9
Total	200*

*DHSS recorded 159 in 1986.

the additional temporary senior registrar posts required for training in community child health.

Registrars

The total number of registrars identified by the BPA survey was 356 (table 4). The discrepancy between this figure and the DHSS total of 287[6] is probably accounted for by the 66 research registrars.

In estimating the future needs for registrars two proposals made in *Plan for Action* must be taken into account[2]: (1) the designation of overseas registrars, who will return to their own countries, as 'visiting registrars'; and (2) the establishment of a quota of 'career registrars', who will be eligible for a hospital career in the United Kingdom, in order to maintain an appropriate balance with senior registrar and consultant posts.

Of the 287 registrars recorded by the DHSS in 1986, 115 were born overseas[6] and the BPA considers that there will be continuing training opportunities for at least 100 visiting registrars. The number of career registrars needed in the period of expansion in the next 10 years, allowing for losses into general practice or other specialties, will be about 250 which, together with 100 visiting registrars, gives a total of 350. As in the case of senior registrars the number of career registrars will fall when the specialty has reached its steady state. These posts could, however, be retained as visiting registrar posts and continue as part of a recognised training programme as there is no manpower restriction on visiting registrar posts.

Senior house officers

The BPA survey showed that of a total of 1080 senior house officers in paediatrics 38% are general practitioner vocational trainees. The number of general practice trainees is likely to rise in view of the importance now attached to paediatric training for general practitioners, and doctors who are planning a career in a specialty other than paediatrics will continue to opt for some paediatric experience and training at senior house officer level. The BPA accordingly foresees a modest rise in the number of senior house officers in paediatrics to about 1200

Table 4 *Numbers of registrars. BPA survey in England and Wales in 1986*

Type of post	*No*
NHS full time	229
NHS part time	11
Honorary (university)	22
Honorary (soft money)	28
Research	66
Total	356*

*DHSS recorded 287 in 1986.

The 'Safety net'

Paediatrics is recognised in *Plan for Action* as one of the acute specialties to be included in the safety net arrangements,[2] which aim to ensure a minimum safe level of resident intermediate staff for 24 hour emergency cover. The provision of an acute service for neonates and seriously ill children in district hospitals requires resident staff with paediatric experience Our manpower proposals would meet this requirement with a one in three rota, using varying combinations of senior registrars, career registrars, visiting registrars, second year senior house officers, and the new staff grade. First year senior house officers are too inexperienced in paediatrics to be included in the safety net staff. As the number of whole time equivalents in the non-training grades in paediatrics are relatively small at present (table 2) it may be necessary to increase the number of posts in the new staff grade to fulfil the safety net requirements in some districts.

Conclusion

At a time when major changes are taking place in the hospital staffing structure and the district child health services are progressing towards integration it was thought essential that the BPA, which is the only organisation with the necessary understanding of paediatric services, should obtain first hand information from local professional sources on all paediatric staff in the country. This exercise in the collection of medical manpower statistics, though time consuming, has proved to be worth while. Based on these reliable data it has been possible to make projections for paediatric manpower for the next 10 years and into the 21st century (table 5).

Table 5 *Proposed future paediatric manpower profile*

Grade	*No*	
Consultants	1490	
Senior registrars	210	
Registrars		
Total	350	
Career		250
Visiting		100
Senior house officers	1200	

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Current topic

Oncogenes in malignancy

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All doctors are familiar with the meaning of the words oncology and genes but most are likely to have been quite puzzled over the last few years as they came upon the new hybrid term, oncogenes, and even more so by its siblings protoncogenes and cellular oncogenes. In this article I will attempt to explain what is meant by the term, how they have been discovered and defined, in what way they relate to normal human genes, how their study has shown the genetic basis of cancer, and make some suggestions for how their analysis could affect the diagnosis and treatment of cancers, particularly those of childhood. Unfortunately, most of this last section will be speculation and gazing into the future but in view of the tremendously fast rate of progress over the last five years it would be unwise to dismiss all such ideas as merely fantastical.

Identification of oncogenes

THE COMING OF CLONING

Oncogenes have been identified over the last few years by scientists working in the fields of virology, cytogenetics, and cell biology: all of them using the techniques of molecular biology and molecular genetics, which have been made possible by the development of recombinant DNA. The cloning of genes or pieces of DNA in recombinant molecules has made it possible to isolate and prepare in bulk DNA sequences that were previously present in such small amounts that they were impossible to purify. These purified sequences can then be used to probe for identical or related sequences in DNA from a variety of sources including tumours. The probing is made possible because the two strands of the double helix of DNA contain complementary sequences and when both probe and target DNA are melted to give single stranded molecules they will reform into a duplex wherever a complementary sequence is found (nucleic acid hybridisation).

The other technical advance which revolutionised the experimental approach to these problems was the discovery of a class of enzymes, found in bacteria, which cut DNA at specific sequences of the base pairs (restriction enzymes). This gave the power to manipulate DNA very specifically and reproducibly.

Research in all the different and apparently non-related disciplines converged in a remarkable way to identify a few related genes.

THE ROLE OF THE VIROLOGIST

The study of tumour viruses in a range of animals (but not in humans until the recent discovery of the human immunodeficiency viruses) has thrown light on both the genes causing transformation and the mechanism by which this can arise.[1] Transforming retroviruses, which have a genome made of RNA rather than DNA, are found in a wide range of vertebrate species including monkey, cat, mouse, and chicken. The types of tumour they can cause also vary widely and include sarcomas, lymphomas, leukaemias, and carcinomas. Fortunately for the experimenter they transform cultured cells as well as rapidly inducing tumours in animals.

A virus normally contains only the genetic information needed for its own reproduction, which an infected cell will copy using its own machinery. An oncogenic virus also contains an 'oncogene', however, which has been transduced from the host organism into the viral genome at some previous point in its history. The structure of the gene will have been altered at the time at which it was picked up by the virus, any non-translated regions which interrupted the original gene on the chromosome (these are normally occurring and are called intervening sequences) will have been removed, and the gene may have been shortened or changed by point mutations. In some cases the virus may have picked up two such genes. It is the production of this abnormal protein by the host cell's machinery which converts it into a cancerous cell.

TRANSFERRING A TUMOUR GENE—THE CELL BIOLOGIST

When DNA extracted from human tumour cells is applied to a culture of the mouse cell line NIH 3T3 some of the cells take up small pieces of DNA and in around 15% of cases a small colony of cells grows out into a clump, a sort of mini tumour. The human DNA can be isolated from these cells by cloning and then analysed. In most cases the isolated gene belongs to a family (of three) genes called ras which had previously been identified as the oncogenes present in the mouse sarcoma viruses Kirsten and Harvey ras.[2] This provides very direct evidence that the alteration in a tumour cell is a somatic mutation of the cell's DNA

THE CYTOGENETICISTS ART

As the methodologies for obtaining good chromosome preparations from tumour cells have improved a wealth of data have been produced on chromosome changes in tumours. In particular it has become possible to correlate chromosome changes with detailed diagnoses, progression of the disease, and secondary tumours. Amazing progress has been made in the cytogenetics of leukaemias and lymphomas but recently, with technical advances, many other tumours including those of soft tissue have begun to show consistent chromosome changes The chromosomal changes observed may be translocations, gain or loss of a complete chromosome, or deletions In the case of leukaemias and lymphomas, translocations have been particularly well defined and the hypothesis has been formed that it is the alteration in the structure or expression of the genes located at the translocation breakpoints which cause at least one step in the cell's progress to becoming cancerous There has therefore been a belief that identification of genes located at these breakpoints will identify further oncogenes This has led to a surge of interest in human gene mapping with many valuable consequences Because of the lack of resolution of most methods of gene mapping, however, it has been extremely difficult to implicate definitely many genes by these methods. The outstanding exceptions are the c-myc gene implicated in Burkitt's lymphoma and the c-abl gene implicated in chronic myelogenous leukaemia and acute lymphocytic leukaemia Both of these will be discussed in detail later.

Cytogenetics has also played the major part in identifying the chromosomal position of and, more recently, facilitating the cloning of genes involved in cancers where there is an inherited predisposition This will be discussed further in the section on retinoblastoma

The nature of oncogenes

HAVE WE ALL GOT THEM?

The cloned oncogenes isolated by the methods described above can be used as hybridisation probes to search for the same sequences in DNA from non-tumour tissue There were several surprises when this was done. It is clear that normal human DNA contains sequences complementary to the oncogene DNA and indeed these sequences are highly conserved throughout evolution. Both these findings suggest that they have normal cellular equivalents, performing essential functions of the cell (because of the high degree of species conservation). These normal equivalents of oncogenes are called cellular oncogenes or c-onc (undoubtedly a particularly misleading and confusing nomenclature) or protoncogenes. Thus the cellular equivalent

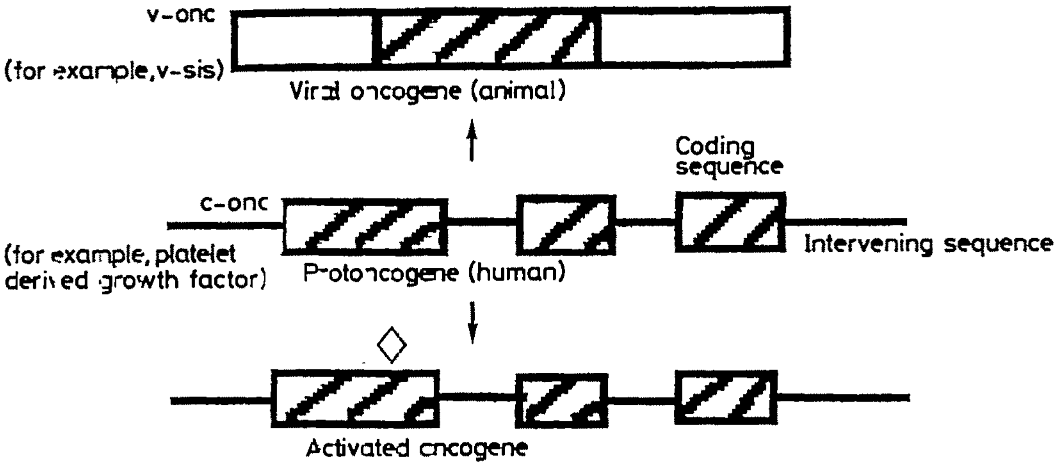

Fig 1 *Relationship between protooncogenes, viral oncogenes, and activated oncogenes*

of the viral oncogene v-myc is called c-myc until the day when somebody identifies the real nature of this gene at which point it will revert to some quite straightforward biochemical name Protoncogene conveys far more satisfactorily the sense that a gene has been identified, which when mutated in various ways has the potential to contribute to transformation of the cell. It is therefore the case that, to paraphrase Molière, we have all been inheriting oncogenes for years without knowing it.[3] The relationships between the different forms are shown in fig 1.

WHAT DO THEY NORMALLY DO?

In only very few cases has the connection between a known oncogene and a biochemically defined human gene been made. This is achieved by comparing the sequence of a viral oncogene (for example) with newly acquired sequence data of human proteins and their complementary nucleotide sequences, making allowance for possible alterations and mutations of the sequence in the virus. In other cases the identity of the protein is still unknown but its site of action and other functional information may be known. The first oncogene whose cellular equivalent was identified was sis. In its viral form v-sis it is a simian sarcoma virus but its human equivalent has been identified as the β subunit of platelet derived growth factor. The table lists the other oncogenes with identified products. In general they appear to be growth factors and growth factor receptors, but any molecule exerting major control over cell growth or division can be considered a potential oncogene. Several excellent reviews expand this information.[4 5]

HOW ARE THEY ACTIVATED?

At least two ways in which the protein amino acid sequence is mutated during oncogene activation are known. In the case of activated ras genes, isolated by transfection experiments, the mechanism is a simple point mutation leading to a single amino acid difference (fig 2). N-ras gene encodes a 21 000 dalton protein whose normal function is to couple growth factor receptors to inositol phosphate production.[6] In the DNA isolated from tumours point mutations affecting amino acid residues 12, 13, and 61 have been found.

Table *Identified oncogenes*

Name	*Human gene*	*Original virus*
c-sis	Platelet derived growth factor	Simian sarcoma virus
c-erbA	Glucocorticoid receptor	Avian erythroblastosis virus
c-erbB	Epidermal growth factor receptor	Avian erythroblastosis virus
c-fms	Macrophage colony stimulating factor	Feline sarcoma virus

ras protein p21

	10 gly	11 ala	12 gly	13 gly
Normal	GGC	GCC	GGC	GGT
Bladder carcinoma			GTC val	

Fig 2 *Mechanism of activation of the Ha-ras gene in bladder carcinoma.*

Secondly, a chromosome translocation such as the 9;22 translocation found in the Philadelphia chromosome in chronic myelogenous leukaemias can bring together parts of two genes that are normally quite separate in the genome. This can result in aberrant mRNA expression and splicing to include sequences from both sides of the breakpoint resulting in a novel chimeric c-abl protein with a molecular weight of 210 000 instead of the normal 145 000 and an altered amino terminal end.

In chromosome rearrangements such as the 8;14, 8;2, and 8;22 translocations found in Burkitt's lymphoma breakpoints occur around and adjacent to the c-myc oncogene altering the expression of the gene, probably by changing mRNA stability, rather than the sequence of the protein.

Over expression of an oncogene can occur because the DNA sequence is amplified many times. Amplification of several oncogenes has been shown but the most interesting, because of its clinical correlations, is N-myc in neuroblastomas. Again there is no change in the structure of the protein product.

Cancers and oncogenes

LYMPHOMAS, LEUKAEMIAS, AND TRANSLOCATIONS

Chromosome translocations are often found in leukaemias and lymphomas and by correlating all these findings at international workshops it is rapidly becoming possible to build up a consistent picture of specific translocations associated with particular tumour types [7] Some of the well established associations are shown in fig 3

The value of these studies is twofold: from the clinical point of view it helps to define subgroups of disease with altered prognosis Thus the child with acute lymphocytic leukaemia carrying a t(4;11) translocation has a particularly 'poor' prognosis. From the scientific point of view it defines the exact region of the chromosome where genes important

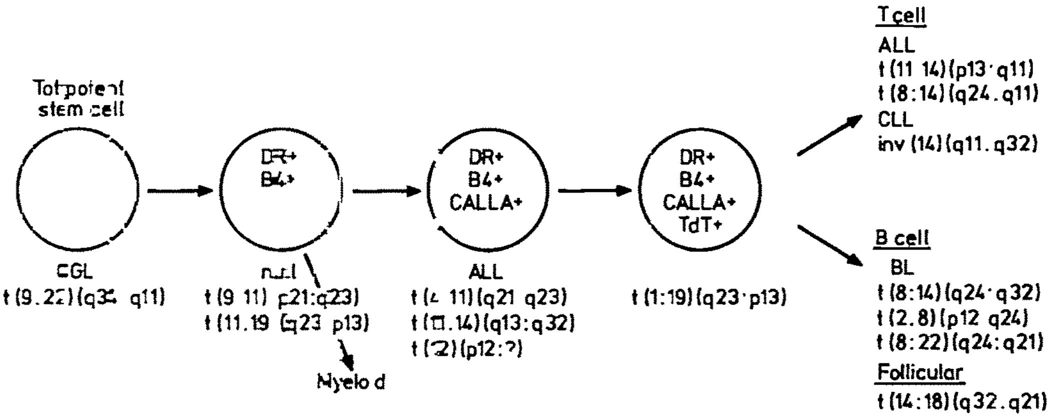

Fig 3 *Specific translocations in malignancies of lymphoid lineage CGL chronic granulocytic leukaemia; CALLA: common acute lymphoblastic leukaemia antigen; Tdt: terminal deoxynucleotidyl transferase; ALL· acute lymphoblastic leukaemia; BL: Burkitt's lymphoma; and DR and B4 are cell surface antigens.*

for at least one stage of the malignant process must reside. Several excellent reviews outlining the various chromosome changes are available.[8 9] Recently considerable progress has been made in delineating the changes in solid tumours.[10]

Although it has been known for many years that the African form of Burkitt's lymphoma carries a t(8;14) translocation, more recently it was shown that variant forms of Burkitt's lymphoma existed with t(2;8) and t(8;22). In each case the breakpoint on chromosome 8 remained the same, at the position of the c-myc oncogene, and in each case the reciprocal translocation corresponds to one of the three immunoglobulin genes (heavy chain, κ light chain, and λ light chain). The DNA of the immunoglobulin genes rearranges to generate antibody diversity during the differentiation of B cells and detailed studies at the molecular level have shown that the translocation arises as a failure of the normal 'recombinase' mechanism. Not surprisingly the translocations in T cell leukaemias have been shown to involve the genes of the α chain of the T cell receptor which rearranges using the same mechanism during T cell development. In this case, however, the oncogene on the other side of the breakpoint has not yet been identified and a reversed genetic approach of cloning the DNA sequences across the breakpoint and then identifying their origin can be used.

Although the Philadelphia chromosome is a marker for chronic myelogenous leukaemia a cytogenetically indistinguishable chromosome is found in 2–10% of childhood acute lymphoblastic leukaemia (Ph$^+$ALL). Molecular analysis has shown that as in chronic myelogenous leukaemia a mutant c-abl gene is created by fusing sequences from chromosomes 9 and 22 but the position of the breakpoint on 22 is different,[11] although interrupting the same gene, and in this case the protein has a molecular weight of 190 000.

NEUROBLASTOMA AND GENE AMPLIFICATION

An amplified oncogene N-myc has been identified from neuroblastomas, both tumour tissue and cell lines. N-myc was identified both by weak hybridisation to the oncogene c-myc, because of some regions of sequence homology, and by molecular cloning of amplified sequences from a neuroblastoma cell line. The amplified sequences show up as homogenously staining regions or double minute chromosomes in cytogenetic preparations from neuroblastoma lines. The frequency and degree of amplification in primary tumours varies greatly. Brodeur and colleagues showed that in 89 primary neuroblastomas amplification varied between three and 300 copies in 34 out of 89 tumours.[12] Amplification was not found in eight stage I or five stage IVS tumours, however, but was found in two out of 16 stage II, 13 out of 20 stage III, and 19 out of 40 stage IV tumours. Progression free survival also correleated with the amount of N-myc amplification. At 18 months, 70% of patients with one copy survived, 30% with three to 10 copies, and only 5% with more than 10 copies. Amplification of N-myc cannot be the primary cause of neuroblastomas as 62% of primary tumours have no extra copies. Its role is probably associated with the progression of the disease and this may be by a fairly general mechanism as amplification has also been found in retinoblastomas, small cell lung cancers, and malignant astrocytomas.

RETINOBLASTOMA AND DELETIONS

Retinoblastoma is representative of a class of embryonic tumours where loss of one of the pair of chromsome alleles by a variety of genetic mechanisms is essential to the development of the tumour.[13] In about 5% of non-inherited forms of retinoblastoma a constitutional chromosome deletion of chromosome band 13q14 has been observed. In familial cases of retinoblastoma there is close genetic linkage between esterase D and the disease. Esterase D maps to 13q14. Both of these observations suggested that the gene predisposing towards retinoblastoma must lie in that band and (as originally proposed by Knudson[14]) loss of the wild type allele exposes the other mutant or deleted allele. This gene has now been cloned[15] and shown to be a nuclear phosphoprotein associated with DNA binding activity.[16] It is not clear that it can be classified as an oncogene, particularly as it appears to be loss of activity which causes the development of the tumour. However, it has increased our knowledge of the genetic mechanisms underlying cancer. Osteosarcomas are common as secondary tumours in cases of retinoblastoma and it has also been shown that chromosome 13 sequences are lost in these.

Wilms' tumour shows a similar relationship with sequences from band 11p13 but no candidate gene has yet been isolated.

Uses of oncogenes

PROBES FOR DIAGNOSIS

Once the breakpoint in a tumour has been defined and cloned hybridisation probes can be produced that are likely to detect rearrangements of the DNA in other tumours of the same type. This could be used diagnostically, probably rather more cheaply than by using chromosomes, or to look for residual disease. An example is the cloning of the sequence on the chromosome 22 side of the Philadelphia chromosome the so called bcr probe from the 'break-point cluster region'.

TREATMENT??

Some examples will occur when study of the state, of either mutation or dosage, of an oncogene will indicate the prognosis in a particular patient and thereby influence the treatment regime. It may even be possible to design drugs which act against the altered specificity of a mutant oncogene or to regulate their expression by injection of an antisense RNA.

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See related article on p 1012

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Personal practice

Management of constitutional delay of growth and puberty

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Constitutional delay of growth and puberty (CDGP) is not a disease but a common condition in which puberty and its associated growth spurt occur at an age which is near the extreme of the normal range. Growth at puberty is intimately related to the stage of pubertal development and this is why, quite appropriately, both growth and puberty are implicit in the name, although it could be argued that they occur in an incorrect order. It is an important condition to recognise as many such children only need reassurance although some will require, if only for psychological reasons, therapeutic intervention to improve their short term growth There is much information available about the anthropometric progress of children with constitutional delay of growth and puberty and we have attempted to correlate this with our more recent understanding of possible options for the manipulation of the endocrinology of puberty.

Definition

Constitutional delay of growth and puberty is defined by Prader as: 'constitutional delay of growth occurring in otherwise healthy adolescents with stature reduced for chronological age but generally appropriate for bone age and stage of pubertal development, both of which are usually delayed'.[1]

As growth potential is related to the degree of epiphyseal maturation, it is this delay in bone age which permits a final stature within the normal range. It is the 'tempo of growth (and puberty) which is significantly delayed.[2] In this article, we shall use the terms 'constitutional delay' and 'growth delay' as synonymous with CDGP as they are almost certainly manifestations of the same condition. although presenting at different ages (see below). CDGP is more common in boys than girls and tends to have a familial pattern. The anthropometric, as well as the psychological. sequelae of delayed puberty are more dramatic in boys on whom we shall concentrate most of our discussion.

Endocrinology of puberty

The initial endocrine event of puberty is high amplitude pulsatile gonadotrophin secretion from the pituitary gland in response to pulsatile gonadotrophin releasing hormone (GnRH) secretion from the hypothalamus.[3] These events occur predominantly at night, as does growth hormone secretion. It is interesting that the secretion of these hormones is intimately related to the night during puberty and that this relationship continues throughout reproductive function; the onset of the luteinising hormone surge in women, which is an essential prerequisite to ovulation, occurs in the early hours of the morning The diurnal secretion of these hormones during early puberty has important implications for their therapeutic administration[4]; oestrogen in girls should be administered in the morning, oral testosterone in boys as well as growth hormone in both sexes are usually given during the evening.

There is a sex difference in the pituitary response to GnRH which may explain the characteristic differences between the timing of the onset of puberty in girls and boys; girls more readily release gonadotrophins to a given GnRH stimulus [5] This may explain why the onset of puberty is earlier in girls than boys, why central precocious puberty is more common in girls, and why constitutional delay of growth and puberty is more common in boys.

Although both sex steroids and growth hormone are required for the growth spurt of puberty, the pattern of secretion of sex steroids alone does not explain the growth acceleration of puberty. In girls, oestrogen secretion is at its peak just before menarche, when the growth spurt is waning. In boys, sex steroid secretion increases progressively throughout puberty and yet initially growth decelerates and the onset of the growth spurt occurs relatively late between genitalia stage 3 and 4. Both sex steroids and growth hormone are synergistic during the growth spurt and it has been appreciated for many years that boys with delayed puberty before the onset of the growth spurt, as well as girls in late prepuberty, have physiological growth hormone insufficiency,[6] which can be reversed by exogenous administration ('priming') with sex steroids.[7] We have recently appreciated, however, that growth hormone pulse amplitude and not sex steroid secretion correlates with changes in growth velocity during puberty in both girls and boys.[8] Short term use of sex steroid 'priming' in boys in early puberty temporarily increases growth hormone secretion, and the administration of sex steroids for greater than three months induces a sustained increase in both growth hormone secretion and growth that continues after the cessation of treatment. This is the principle for short course treatment with anabolic and sex steroids for boys in early puberty with CDGP

Data from postmortem examination,[9] pelvic ultrasound,[10] and hormone profiles[5] have suggested that the endocrine events which we associate with puberty probably have their origin very much earlier in childhood. Gonadotrophin secretion progressively increases throughout childhood and when sufficient sex steroids are secreted to induce secondary sexual characteristics, then phenotypic puberty begins. These low concentrations of sex steroids secreted during early childhood, however, may have great significance for the physiology of growth delay. After the second year of life, when growth has become dependent on growth hormone,[6] low concentrations of sex steroids may result in secondary growth hormone insufficiency and low growth velocity but with contemporaneous retardation of epiphyseal maturation; this is the exact scenario observed in growth delay.

Pubertal development

It is important to distinguish puberty that is normal, except that the onset is delayed, from absent pubertal development or arrested puberty (no progress for 18 months or more). In contrast to CDGP, hypogonadotrophic hypogonadism is a spectrum which may present clinically as absent puberty, arrested puberty, or failure to attain reproductive function depending on the degree of GnRH insufficiency. Thus children who have *no* signs of puberty at 2·5 SD or greater from the mean (14·0 years in a girl and 14·5 years in a boy) require appropriate endocrine and radiological investigation of the hypothalamo-pituitary axis.

Progress through puberty can take a considerable length of time, 3% of normal girls and boys take longer than five years to progress from genitalia/breast stage 2 to 5.[11 12] For example, a boy who enters puberty at 14 years may not complete his puberty (and therefore his growth) until 19 years and perhaps considerably later as children who enter puberty later tend to progress through puberty more slowly.[1]

Pattern of growth

CDGP is more common in boys than girls for reasons we have discussed. Even when this becomes a clinical problem in a girl, it is self limiting because as soon as the onset of puberty occurs (breast development) and they commence their growth spurt, girls will attain peak height velocity between breast stage 2 and 3. By contrast, the problem is exaggerated in boys because their growth spurt only occurs towards the end of puberty. The growth spurt commences at 10 ml testicular volume (genitalia stage 3 to 4) and attains a peak velocity at 12 ml (genitalia stage 4 to 5). Thus the growth of a boy who enters puberty at 14 will continue to decelerate for many years, until the growth spurt starts at perhaps 17 or 18 years of age, by which time he is considerably shorter than his peers. The later the growth spurt occurs, the lower the peak height velocity that is attained, as final height attainment is not dependent on the timing of the onset of puberty (except in precocious sexual development).[13 14] This dictum has recently been affirmed as the use of a GnRH analogue to delay the puberty of short normal children does not improve final height prognosis.[15]

An example of a boy with CDGP is shown in fig 1. Although he entered puberty at 14 years, his growth continued to decelerate at an extended 50th centile velocity. This may imply a growth velocity of only about 2–4 cm/year by the age of 16 years, and although this may induce considerable concern in his medical attendants it is important to appreciate that this is normal for chronological age and stage of puberty. By the age of 16 years, at the commencement of the growth spurt, his height was 15 cm below the 3rd centile on the 'distance' chart

Diagnosis of constitutional delay of growth and puberty

The characteristic feature of normal puberty is that there is a relationship between the pattern of acquisition of the various stages of sexual maturation and the growth spurt. Loss of this normal harmony of growth and puberty points to an

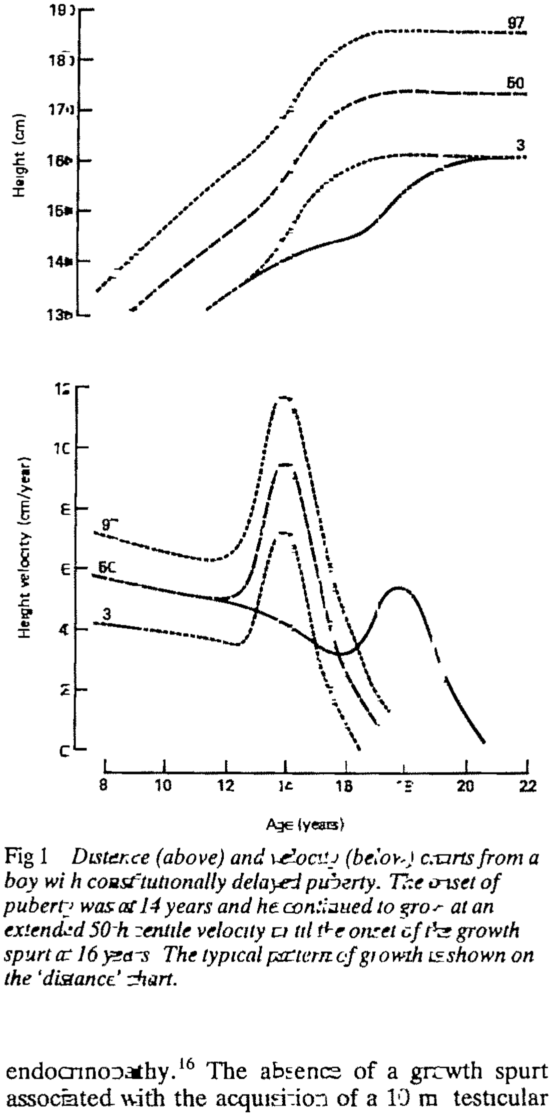

Fig 1 *Distance (above) and velocity (below) charts from a boy with constitutionally delayed puberty. The onset of puberty was at 14 years and he continued to grow at an extended 50th centile velocity until the onset of the growth spurt at 16 years The typical pattern of growth is shown on the 'distance' chart.*

endocrinopathy.[16] The absence of a growth spurt associated with the acquisition of a 10 ml testicular volume; a growth velocity of 2 cm/year in a boy in early puberty that is appropriate at 17 years but not at 13 years; and a large testicular volume in relation to inadequate virilisation are all examples of loss of the normal harmony of growth and puberty and necessitate investigation. In contrast, the normal consonance of growth and puberty is usual in children with CDGP and thus mitigates against special investigations.

Growth delay often occurs in children with severe systemic disease such as asthma, renal disease, coeliac disease, inflammatory bowel disease, or after the chronic use of corticosteroids It is important not to overlook these possibilities as they can mimic some of the features of CDGP[7]

The distinction between CDGP and partial hypogonadotrophic hypogonadism can be difficult as both show the normal consonance of growth and development. In order to distinguish between these two conditions puberty may have to be induced (see below) for a period of two to three years and then progress observed after the cessation of treatment. Congenital growth hormone insufficiency is not usually confused with CDGP because by this age children with the former are very much shorter than the latter. Acquired growth hormone insufficiency secondary to an intracranial tumour, however, must always be considered. In girls, Turner's syndrome and its variants should be excluded by a karyotype. Children with primary hypothyroidism usually have a growth rate that is inappropriately low for their age and stage of puberty, and moreover may have inappropriate sexual maturation.[16] Children with mild skeletal dysplasias, such as spondyloepiphyseal dysplasia seldom have a delayed bone age and usually exhibit limb-trunk disproportion. The diagnosis is confirmed by skeletal survey.

If pharmacological tests of the hypothalamo-pituitary axis are carried out these usually require sex steroid 'priming' (see above) and, in the clinical situation of delayed puberty, are difficult to interpret. In our experience the anthropometric data are more reliable. If sex steroid 'priming' is required, however, then it is appropriate to use stilboestrol (1 mg twice a day for three days), which can be used in either sex and does not interfere with the anthropometric data

Psychological sequelae

The delay of both growth and puberty can have considerable psychological sequelae, especially because this is such a critical time for social, emotional, and educational development and, importantly, the onset of relationships with the opposite sex. At no other time during life is peer group pressure so important and influential than at adolescence. In an analogous way to facial acne, there is little consolation in the advice that all will be well if the boy waits long enough and that growth will be complete in his early 20s. This is highlighted by the following extracts from a letter written by an intelligent 17 year old boy with delayed puberty.

> '... I often get very upset, but I find it very difficult to release my tension. When I do, this results in huge arguments, often over petty inconsequential things. I do not wish to be told to leave pubs, and 'X' certificate films when I am 18. I lose a great deal of my confidence with girls—I feel fine talking to them normally, but asking to go out with someone is something I

> wouldn't consider, as I can't understand many 17 year olds wishing to go out with someone who looks like a 14 year old. It is certainly difficult for me to convey how I feel, but all I can say is that I feel utterly powerless, and I often feel quite depressed over this matter This, I fear, will begin to affect my work which is very important as I am approaching my 'A' Level examinations'.

This summarises many of the difficulties that such boys commonly experience, although it is unusual to have such depth of insight. Many boys with CDGP are subject to bullying and some develop antisocial behaviour such as shoplifting or vandalism, which may bring them into conflict with the authorities They require therapeutic help and not unnecessary investigation. It is surprising that when boys with CDGP are asked whether growth or puberty is their primary concern, most indicate the former and it is to this aspect that the therapeutic approach should be aimed.

Treatment of constitutional delay of growth and puberty

The most important decision is whether, rather than how, to treat a boy with CDGP. This is only indicated when such a boy is experiencing psychological distress. It is important to have the parents present at the initial interview as events such as bullying are more likely to be alluded to by the parents because the admission of this by an adolescent boy may be considered as a sign of weakness. Often the attendance of the adolescent and the discussion about such delicate problems, as perceived by the adolescent, at a clinic appointment is a significant sign in itself.

It is important to emphasise that this condition is just a variation of the normal timing of puberty, and is not an illness. This also indicates the necessity for an effective but safe treatment. Misconceptions about future fertility and manhood may require reassurance It is unlikely that treatment will improve final height, although this is theoretically possible using growth hormone treatment, but it will allow the boy to achieve final height at an earlier age.

Two therapeutic approaches in the treatment of CDGP are possible. Either the growth spurt can be induced using a low dose of an anabolic steroid or possibly growth hormone, with little alteration in the progress of sexual maturation, or puberty can be induced along with its associated growth spurt by the administration of testosterone or human chorionic gonadotrophin.

ANABOLIC STEROIDS

These have been extensively used for the past three decades in North America but unfortunately their initial use was in high dose regimens for long periods which resulted in side effects of hepatotoxicity,[18] suppression of the hypothalamo-pituitary-gonadal axis,[19 20] and inappropriate advance of epiphyseal maturation.[18] Sobel noted that virilisation is dose dependent, whereas the growth acceleration was not.[21] Low doses of anabolic steroid[22 23] administered orally in a daily regimen induce a growth spurt that is not a placebo effect.[24] At the attainment of a 4 ml testicular volume this growth acceleration is sustained, and therefore only relatively short courses are required [22 23] At the cessation of treatment this induced growth spurt continues and eventually becomes indistinguishable from the spontaneous growth spurt of puberty at the attainment of a 10 ml testicular volume (fig 2). Such low dose regimens do not cause inappropriate advance in epiphyseal maturation and do not alter final height prognosis.[22 23] There is a normal advance in secondary sexual characteristics during such short course, low dose regimens of anabolic steroids and testicular volume is not suppressed. Unfortunately, despite the usefulness of anabolic steroids in the treatment of constitutional delay and other growth disorders, fluoxymesterone is now unavailable and oxandrolone can only be prescribed on a 'named patient basis' as it has no product licence in the United Kingdom.

TESTOSTERONE AND HUMAN CHORIONIC GONADOTROPHIN

An alternative approach is to induce secondary sexual characteristics and thereby their associated growth acceleration by using either testosterone or human chorionic gonadotrophin. Testosterone is usually administered by deep intramuscular injection of a depot preparation at monthly intervals or orally, as testosterone undecanoate, during the evening.[4] Unfortunately such oral preparations have variable absorption from the gastrointestinal tract that limit their usefulness. Depot testosterone esters are certainly effective,[25] although unfortunately they are often used in excessive doses, but they probably do not reduce final height attainment.[26] Although testosterone administration suppresses the hypothalamo-pituitary-gonadal axis, with reduction in testicular volume, this is only temporary. Testosterone treatment often produces a rapid rise in serum testosterone concentrations and also wide fluctuations in concentrations between injections which can, in themself, produce emotional lability and may become counterproductive to the indications for treatment. An alternative and

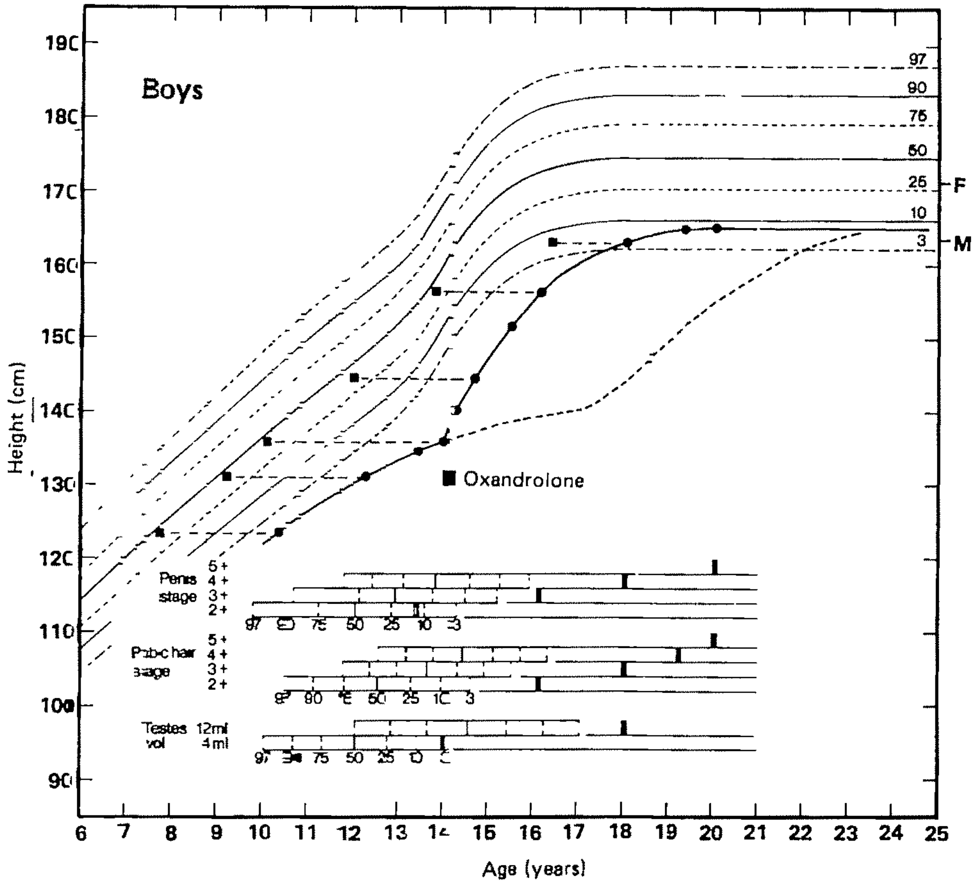

Fig 2 *Growth data from a boy with constitutional delay of growth and puberty. Bone age is shown by the solid squares Parental centiles are indicated on the right hand border His expected pattern of growth is indicated by the dotted line. At the age of 14 years he was treated with a three month course of oxandrolone (1·25 mg daily), and the induced, sustained growth acceleration became indistinguishable from the growth spurt of puberty at the attainment of a 10 ml testicular volume*

more physiological treatment is human chorionic gonadotrophin, but this has to be administered in two to three injections a week, which limits its use. Both testosterone and human chorionic gonadotrophin need to be given for a minimum of three months in order to attain a sustained growth spurt. Of course, unlike anabolic steroids, both testosterone esters and human chorionic gonadotrophin have to be given by injection.

For girls who require treatment low dose oestrogen, such as ethinyl oestradiol 2 μg daily, can be administered as this induces a growth acceleration. When an advance in puberty has occurred which is inappropriate for the dose of exogenous oestrogen, then the medication can be withdrawn with the probability that spontaneous puberty has started. Human chorionic gonadotrophin cannot be administered in girls because of the likelihood of ovarian hyperstimulation syndrome.

GROWTH HORMONE

From the discussion about the mechanism of the growth spurt of puberty, it is not surprising that the administration of growth hormone can improve short term growth in boys with CDGP[27] and this could theoretically improve their final height prognosis Because of the increase in growth hormone secretion which occurs during puberty, however, larger doses may have to be used than are administered in the treatment of growth hormone deficiency in prepubertal children.[28] From experience of the management of children with hypopituitarism, growth hormone treatment has little effect during late prepuberty. Treatment is expensive and may have to be continued for a long period of time because of the possibility of 'catchdown' growth[29] Growth hormone is certainly not the primary choice of treatment for children with CDGP; as they have physiological growth hormone insufficiency it seems more appropriate to use an androgen in boys or an oestrogen in girls to induce increased endogenous growth hormone secretion.

A practical regimen

The normal harmony of puberty is the characteristic of CDGP. Indeed, endocrine investigations in delayed puberty are notoriously difficult to interpret and are more often misleading than they are helpful. Most patients with psychological distress due to CDGP require an effective safe treatment, rather than investigations. If puberty is disordered or if there is an inappropriate anthropometric response to treatment,[30] however, then the patient should have neuroradiological and endocrine assessment of the hypothalamo-pituitary axis.

Once the diagnosis has been made then reassurance should be given and treatment only offered if there is inappropriate psychological distress. For boys with CDGP for whom short stature is the predominant symptom, then treatment should be given with an anabolic steroid such as oxandrolone 1·25–2·5 mg daily for three to four months. This will induce a growth spurt which, after the attainment of a 4 ml testicular volume, will be sustained. If growth deceleration does occur on cessation of anabolic steroid treatment, then a further three to four month course can be administered. Once a sustained growth spurt is achieved then growth and development should continue without requiring any further treatment. It is important to explain that this treatment is only advancing the timing of the growth spurt without altering final height attainment. In the more unusual case where inadequate sexual development is the predominant symptom then treatment with testosterone esters (such as Sustanon 50) should be administered at monthly intervals for three to four months. Usually, this is sufficient to induce an advance in pubertal maturation with concomitant growth acceleration.

Growth delay can often be recognised many years before puberty and the growth pattern of CDGP can be anticipated and effectively prevented. In the prepubertal years and before the attainment of a 4 ml testicular volume, low dose anabolic steroids will induce a growth spurt but this will not be sustained. A course of anabolic steroids, such as oxandrolone 1·25 mg daily, can be administered for a period of about a year without inducing sexual development or inappropriate epiphyseal maturation. This regimen will improve short term growth, allowing the boy to attain a higher centile on a 'distance' chart.

Growth hormone and human chorionic gonadotrophin have little place in the management of CDGP, particularly as both have to be administered by frequent injection and the former is very expensive.

Conclusion

Constitutional delay of growth and puberty should be recognised clinically and not require endocrine investigation. Treatment by either anabolic steroids or testosterone should only be given when psychological distress is encountered, but the treatment can be administered by either a paediatrician or community paediatrician without the necessity for referral to a specialised growth centre. However, assessment of epiphyseal maturation is essential in the management of children with delayed puberty. Rarely, when inadequate growth acceleration with treatment is observed, referral to a specialist centre is indicated.

We are grateful to Professor HS Jacobs, Middlesex Hospital, London, for allowing us to use clinical data from one of his patients

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Archives of Disease in Childhood, 1988, **63**, 1111–1116

Correspondence

Copper deficiency and non-accidental injury

Sir,

We write to congratulate Dr Jonathon Shaw on his comprehensive and balanced review of copper deficiency in infancy and its relation to fractures diagnosed as non-accidental injury.[1] We trust that it will put an end to poorly supported attempts on the part of some expert witnesses to ascribe fractures to copper deficiency in circumstances when it is manifestly not present. These attempts have been the subject of adverse comment in the Appeal Court[2] and Family Division of the High Court[3] in both criminal and wardship proceedings The waste of time, money, and emotional damage which results from the protracted and complicated legal proceedings is incalculable

Dr Shaw together with Dr Carty,[4] in the same issue of your journal have established clearly the criteria which should apply before the diagnosis of copper deficiency is considered possible and have shown that proper analysis of clinical, radiological, and laboratory criteria even in the absence of serum copper concentrations are quite adequate in most cases. It is our view, borne out by the data and arguments presented by Drs Shaw and Carty, that infants who sustain fractures but do not have recognised risk factors for copper deficiency, have normal bone structure, and no haematological abnormalities do not need to have copper and caeruloplasmin concentrations measured on clinical grounds It is questionable whether it would be ethical to do them for purely forensic reasons in the absence of reasonable evidence suggesting that they might be abnormal. We are concerned at the prospect of multiple requests for serum copper determination It would be unfair both to the infants and the laboratories

While we accept that premature infants may represent a special risk group because of diminished hepatic copper reserves, many of the references cited by Shaw involve infants given outmoded parenteral feeding formulae or receiving partial enteral feeds With the use of modern crystalline amino acid parenteral feeding solutions together with a trace element solution (supplying 0·3 μmol/kg/day of copper) we have found copper deficiency rare.

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Urinary creatinine excretion in the newborn

Sir,

Al-Dahhan *et al* claim that their data are only the second to report the urinary excretion rate of creatinine in preterm infants,[1] and are apparently unaware of our 1985 paper which theirs closely mimics.[2]

We measured the urinary excretion rate of creatinine in babies of similar gestational ages (26 to 40 weeks), weights (640 to 3710 g), and postnatal ages to Al-Dahhan *et al*, and produced almost identical results and conclusions. We found that the rate varied with weight, surface area, length, gestational age, and postnatal age, but that the relation with body weight was the most powerful, so that there was no correlation between urinary excretion rate of creatinine/kg and most of the other parameters. The only difference between our findings is that we found the urinary excretion rate of creatinine/kg to be slightly higher in the first week of life than subsequently We presented these results as arithmetic means (SD) in nmol/kg per minute. Converting to μmol/kg daily our values of 104 (24) in the first week of life and 95 (19) subsequently were almost identical to the overall figure of 95·7 (33·3) reported by Al-Dahhan *et al*

Al-Dahhan *et al* argue that a knowledge of the urinary excretion rate of creatinine should allow the urinary excretion rates of other substances to be estimated without the need for timed urine collections; in our paper we showed this to be the case for sodium and potassium. Although the 95% confidence intervals for these estimations are wide at 62 to 161%, we have found them to be narrow enough to provide useful clinical information. Using our data, the daily excretion rate of a substance, x, per kg is 104 Ux/Uc for infants in the first week of life and 95 Ux/Uc for older neonates, where Ux is the urine concentration of the substance in units/l and Uc is the urine creatinine concentration in μmol/l. We proposed that for clinical usage the formula 100 Ux/Uc would be more easily memorable with little loss of accuracy. We feel that the data of Al-Dahhan *et al* further strengthen our conclusion

Using the same principle, we also showed that the urine flow rate per kg can be estimated with a similar degree of accuracy from a knowledge of the urinary excretion rate of creatinine/kg and the creatinine concentration of an untimed ('spot') urine sample. The daily urine excretion (ml/kg) is thus 104/Uc in the first week of life or 95/Uc thereafter, or can be approximated to 100/Uc for convenience, but it must be noted that in this case Uc is the urinary creatinine concentration in *mmol/l*.

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Patient triggered ventilation in premature neonates

Sir,

Greenough and Greenhall[1] recently reported their experience of the trigger ventilator.[2] They modified our original circuit by switching the inspiration detector from its site on the abdomen to the oesophagus. We had considered this approach but felt that it had a limited role because it could not be used on a routine basis by untrained staff In their paper they allege that 'gross body movements made the abdominal sensor prone to false triggering. This has never been a problem in my experience over the last three years. While it is obviously theoretically possible to interfere with the signal from the capsule, in practice the design of the circuit largely eliminates this problem. This is best illustrated by the example of an infant on triggered ventilation with an inspiratory time set at its recommended 0·5 seconds. When a breath occurs there is a delay of up to 100 msec before the trigger fires The ventilator is refractory to further signals from the time of firing, through the inspiratory time setting (0·5 seconds) and for 0·25 seconds after this interval (to allow enough time for expiration). Most infants breathe at 60 breaths (approximately) per minute with this inspiratory time (unpublished work) Thus on average the ventilator is refractory for 0·85 seconds out of the 1 second between breaths and only 0·15 seconds remain as a susceptible period before the next breath is due The only consequence of such a false signal is to make the next breath occur fractionally early

I submit therefore that the criticism of our original approach is invalid and that triggered ventilation using an abdominal sensor is an effective means of assisting the newborn's respiratory effort.[3]

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Infective endocarditis in neonates

Sir,

We read with interest the recent review of five patients with neonatal infective endocarditis by O'Callaghan and McDougall[1] We wish to report a further case where echocardiography had an essential role in the early diagnosis of pericarditis and endocarditis in a newborn infant where clinical signs specific to endocarditis were absent

A boy weighing 3200 g was born vaginally at term to a primagravida who had loose bloody stools due to *Shigella sonnei* infection during the last trimester of pregnancy The infant developed shigella enteritis with intermittent gaseous abdominal distension Ultrasound examination showed an abdominal abscess but during this procedure the pericardial effusion was incidentally detected Although the infant was ill and looked septic, arterial pulses and blood pressure were normal The heart sounds were normal with no evidence of a murmur or pericardial rub The chest radiograph showed cardiomegaly but the electrocardiogram was normal A septic spot was noted on the sternum. A peripheral blood count showed thrombocytopenia but no petechial lesions were present There was no haematuria.

Cross sectional echocardiography confirmed the presence of a large anterior pericardial effusion as well as a vegetation on the anterior leaflet of the mitral valve. Thirty ml of pus was obtained by needle aspiration of the pericardial space. Subsequent surgical exploration was performed and the pericardial space was left on continuous drainage for one week An identical strain of *Staphylococcus aureus* was isolated from the pericardial fluid, blood cultures, and the septic lesion on the sternum Gentamicin and cloxacillin to which the organism was sensitive were given intravenously for six weeks. After one week of treatment the pericardial effusion had resolved but the vegetation persisted Umbilical arterial or venous lines were not used at any time during his management He was discharged from hospital at the age of 3 months At that time his cardiac examination was normal, in particular there was no evidence of mitral valve insufficiency Echocardiography confirmed persistence of the mitral valve vegetation which had become more echodense and possibly calcified After discharge from hospital the infant was lost to follow up

Clinical detection of bacterial endocarditis in the newborn who is already ill from sepsis is difficult Embolic phenomena, congestive cardiac failure, and changing heart murmurs are important clues but are infrequently found.[2] Cross sectional echocardiography permits earlier diagnosis of endocarditis provided vegetations are at least 2 mm in diameter[2] We surmise that survival of our patient was due to early diagnosis and prompt treatment with appropriate antibiotics in high doses, and the maintenance of normal tissue perfusion and blood pressure in the presence of overwhelming septicaemia We concur with O'Callaghan and McDougall in the usefulness of echocardiography in the diagnosis of neonatal endocarditis We have shown that with early diagnosis recovery is possible

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Varicella gangrenosa

Sir,

We read with great interest the account of a case of varicella gangrenosa by Kidney *et al*[1] and would like to report our experience with a similar case associated with an unusual complication.

Case report

A 3½ year old girl developed pain in her left leg eight days after chickenpox, when her chickenpox lesions were actually drying up. A couple of days later her parents noticed a few large, dark bruises appearing on her left leg On examination she looked rather pale with a normal pulse rate and blood pressure. She had three large, dark, and tender ecchymotic areas on her left leg and similar, smaller lesions, one on each side, just above the ankle. The left leg was obviously swollen and she was unable to bear weight on that leg Her peripheral pulses were normally palpable.

Initial investigations showed a mild anaemia (haemoglobin 100 g/l) with normal white cell and platelet counts. The prothrombin activity was reduced to 70%. Cephalin-kaolin time increased to 52 seconds and fibrinogen degradation products were >40 mg/l (normal <10 mg/l)

Despite fresh frozen plasma (10 ml/kg) her bruises increased in size in the 24 hours after admission. She was, therefore, started on prednisolone 2 mg/kg/day which seemed to control the spread of the skin lesions and the leg swelling. Her steroid dose was reduced, from the fourth day after admission, but on the fifth day she suddenly developed severe abdominal pain requiring a pethidine injection. She had tenderness in both renal angles and urine examination showed a few red blood cells but no protein. An intravenous pyelogram showed enlargement of both kidneys (left more than right). The right nephogram appeared immediately, the left slowly evolved over 5–10 minutes and the pyelogram on the left was also delayed, beginning to appear after 20 minutes. These findings added support to the clinical suspicion of a renal vasculitis and, probably, a renal vein thrombosis.

She failed to pass urine for 10 hours but, subsequently, produced urine normally. Blood pressure, urea, and electrolytes also remained normal. Plasma proteins and complement concentrations were normal and antiDNA antibodies were negative. Her symptoms quickly improved with intravenous dextrose saline infusion to maintain hydration, continued use of steroids, and intravenous ampicillin. We did not give anticoagulant treatment. The skin lesions became blistery after a few days; this was followed by thick eschar formation This needed application of streptokinase-streptodornase to remove the scab. It took about six weeks for the lesions to heal completely and they had left rather unsightly scars on the left thigh, tethered down to the underlying fascia

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Very young children and the Family Fund

Sir,

When the Family Fund, which gives modest grants to families with severely handicapped children, started in 1973 its advisers almost ruled that no child under 2 years of age could satisfy the medical criteria.[1] Fortunately the possibility was left open and a small number of multiply handicapped babies, being nursed at home, have always been accepted.

In recent years, however, the Fund is receiving applications for and accepting as eligible an increasing number of such babies. In 1981 there were 920 applications on behalf of children under 2 and 50% of these infants were regarded as sufficiently handicapped to be eligible. By 1987 the number of applications had almost doubled and two thirds of them were accepted.

Developments in medical techniques and the increased possibility of litigation if a consultant is not seen to do his utmost to save life mean that more babies born with disabilities are surviving, and more who are born prematurely survive but develop disabilities in their struggle to hang on to life. More significant, from the point of view of the Family Fund, is the fact that such babies are often returned to the care of their parents, even when they require 24 hours nursing.

Research evidence has shown that there are considerable financial costs in caring for a disabled child at home,[2] and the government, in recently announcing the possible extension of attendance allowance to children under 2, has acknowledged that the actual problems of care of such a child are significantly more than that of a normal baby.[3] It is vital that professionals should realise that the Family Fund has always recognised this and that families are not discounted because the child is not yet 2 years old

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Computed tomography in childhood epilepsy

Sir,

Children attending the school at the David Lewis Centre for Epilepsy are a selected group, as with few exceptions they are residential pupils from various parts of the United Kingdom and therefore are likely to have severe and often multiple handicaps. It seemed probable that a group of such children might show a high incidence of significant abnormalities on computed tomography.

The children attending the school at the David Lewis Centre and examined by computed tomography over several years numbered 222; there were 154 boys and 68 girls, aged 7 to 19 years. The results showed that 152 were normal. There were 28 with evidence of some degree of generalised atrophy and 30 with focal atrophy. Nine showed calcification and in three the findings were compatible with a cerebral tumour Abnormalities in a third of the children is in agreement with the findings of Bachman *et al*[1] and Yang *et al*.[2] Bachman *et al* studied 98 children with chronic seizure disorders, and computed tomograms identified structural abnormalities in 30%, almost half having generalised or focal atrophy. Two per cent showed possible evidence of unsuspected cerebral tumours. In the study of Yang *et al*, 256 computed tomograms were performed to aid the evaluation of children with seizure disorders There were abnormalities in 33% that were found mainly among those with partial seizures and generalised seizures of known aetiology, but also in those with neonatal seizures and in those with abnormal neurological findings and focal slowing shown on electroencephalography Five patients were found to have cerebral tumours, one a porencephalic cyst, and one extraventricular communicating hydrocephalus The use of computed tomography among children with non-specific mental retardation also seems to be unhelpful[3] but when the mental retardation is associated with infantile spasms the scan is often abnormal, showing evidence of tuberous sclerosis or agenesis of the corpus callosum.[4]

Therefore it seems unlikely that a selected group of children such as those attending a special residential school will show more abnormalities than those seen in hospital outpatient clinics. Also the use of routine computed tomography in the investigation of children with epilepsy seems unjustified, although it will be indicated if there are symptoms and signs suggestive of a focal lesion. Twenty two children who showed thickening of the skull vault, and often proliferation of the intracranial sinuses, and 25 children with evidence of cerebral atrophy were assessed for correlations with the antiepileptic drugs that had been given and with the possible timing of the damage to the brain Phenytoin and carbamazepine had been given to an equal number in both groups, which did not support the role of these drugs in causing thickening of the skull bones The onset of seizures was more frequent during the first year in the first group, which may suggest an impairment of cerebral development at an early stage, which is also indicated by the thickening of the bones.

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Henoch-Schönlein purpura secondary to trauma

Sir,

The aetiology of Henoch-Schonlein purpura (HSP) is controversial. Various bacterial and viral infections together with drug and food sensitivity have been identified as possible aetiological factors.[1] No mention of trauma as a causative agent has been found in the literature It is postulated that a traumatic event produces a shower of antigenic material of joint contents or tissue breakdown products which may initiate HSP

We describe two cases where trauma preceded the symptoms of HSP.

Case reports

CASE 1

A 2 year old boy was brought to casualty with a limp after a fall the previous day. He had a swollen and tender right ankle. Radiological investigation showed an undisplaced fracture of the metaphysis of the right fibula. He was treated conservatively and later discharged. Two days later he returned to casualty with a painful left ankle. He was irritable, his temperature was 37·1°C, and he had a maculopapular rash HSP was diagnosed and subsequently he developed abdominal discomfort, lymphadenopathy, proteinuria, and purpura. The bruise overlying his right ankle was yellow whereas the purpura of the HSP were blue/black.

CASE 2

A 10 year old boy presented to the surgery of his general practitioner with a two day history of a painful left ankle after a boy had stamped on it. This had been treated initially by the school nurse. In addition he had a swollen painful right ankle which had developed on the day of presentation after a cross country run. Radiological investigation showed no bony injury.

When he was reviewed the next day the bruising to the ankles had developed into a purpuric rash which later spread to his legs and buttocks. HSP was diagnosed and he was admitted to hospital.

Chance association between trauma and HSP is always a possibility but on discussing these cases it emerged that the general practitioner (RC) had encountered two families with a high incidence of HSP sometimes related to trauma One family had two brothers with HSP, one of whom had developed his HSP after a territorial army exercise in Germany. The second family had a grandfather who used to drive a steam lorry. This carried guns from Vickers Armstrong Newcastle to the ship yards on the Firth of Forth. There was a steep bank on this route at Berwick where the lorry required vigorous stoking. On several occasions while being so occupied he would develop severe pain in the ankles and a purpuric rash on his lower legs which at the time he attributed to the heat from the open boiler door!

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Immunoglobulins in very low birthweight premature infants

Sir,

Conway *et al* reported on the immunoglobulin supplementation of very low birthweight (VLBW) neonates.[1] The IgG concentrations measured in the control group were, however, considerably higher than those reported for preterm babies born between the 29th and 32nd weeks of gestation.[2] The higher absolute values might have originated from the different methods of determination and statistical analysis Nevertheless, not only were the absolute concentrations higher but also the postnatal relative decrease in IgG concentration was less marked than expected

These differences are especially interesting for us as in our unpublished follow up investigation on VLBW neonates we also found unexpectedly high immunoglobulin concentrations. As practically all VLBW neonates require at least one packed red cell transfusion in the neonatal period, so one possible factor in the background of a higher immunoglobulin concentration may be the influence of transfusions

In order to elucidate whether packed red cell transfusions can alter immunoglobulin concentrations we measured the immunoglobulin content of 15 blood units used for transfusing babies of mean (SD) postconceptional age of 32·5 (3·4) weeks and postnatal age of 27 (13) days. The following concentrations were found (mean (SD)): packed cell volume, 60·1 (1·2)%; IgG, 10·0 (3·4) g/l; IgA, 1·43 (0·70) g/l; and IgM, 1·3 (1·65) g/l.

By knowing the amount of blood transfused (15 ml/kg) and the pretransfusion packed cell volume of the recipients, and by estimating the circulating blood volume to be 85 ml/kg[3] the impact of the transfusion on serum immunoglobulin concentrations could be calculated. One packed cell transfusion theoretically increased the IgG concentration by 0·93 (0·40) g/l, IgA by 0·14 (0·09) g/l, and IgM by 0·12 (0·15) g/l. Certainly, after extravascular distribution of the immunoglobulins the effect is less marked, however, presumably still not negligible.

It is suggested that in VLBW neonates the 'normal' immunoglobulin concentrations reported may reflect not only endogenous production but exogenous intake by means of the transfusions as well.

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Cardiovascular collapse after verapamil in supraventricular tachycardia

Sir,

Kirk *et al* report the occurrence of severe hypotension and death after treatment of paroxysmal supraventricular tachycardia with verapamil.[1] The fact that digoxin was also employed in three of the five cases is ignored The interaction of verapamil and digoxin and their potential for producing in concert serious adverse effects and even death were reported previously.[2] Likewise, it is important to emphasise the authors' caution regarding the unpredictable effects of the combination of verapamil and propranolol

lol which might also be used in the treatment of supraventricular tachycardia.[3]

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British Paediatric Association

Report from the British Paediatric Surveillance Unit

This is the second report on the activities of the British Paediatric Surveillance Unit (BPSU) to be published in this journal. The first described the background, methodology, and results of the first 12 months of operation (July 1986–June 1987).[1] This report summarises the results of mailings between July 1986 and January 1988.

Cases reported

The table shows, for each of the conditions, the total number of reports received in months 1–19, and the proportion of cases which on detailed follow up (as at 7 April 1988) satisfied the diagnostic criteria. The cases not confirmed include duplicates, reporting errors, and patients who either did not strictly meet the studies' diagnostic criteria or who had their diagnosis revised as a result of further investigation. The last two categories were particularly prevalent among reports of Reye's syndrome and of paediatric AIDS. Among the former nearly half of the cases reported with onsets in the surveillance year 1 August 1986–31 July 1987 had a later diagnostic revision, most frequently to one of the inborn errors of metabolism that mimic Reye's syndrome, such as fatty acid oxidation defects or urea cycle disorders. In the AIDS/HIV illness category, children were reported who had both serological evidence of HIV infection and were symptomatic but whose clinical condition did not meet the United States Centers for Disease Control case definition for paediatric AIDS.[2]

These observations illustrate the need for meticulous and often detailed follow up of case reports. Surveillance of very rare disorders, unlike that of common ones such as measles or pertussis, requires a high order of sensitivity and specificity of case ascertainment and case definition if accurate epidemiological inferences are to be drawn. Follow up is often demanding of the time of the reporting clinician: the success of the BPSU and the acquisition of knowledge about the rare disorders shown in the table is attributable to the goodwill and cooperation of British Paediatric Association (BPA) and

Table *BPSU: reports received July 1986–Jan 1988 (months 1–19)*

Condition	*Total reports*	*Outcome of follow up by investigator*		
		Outcome known		*Not yet known‡*
		Report confirmed (% of known)*	*Report not confirmed†*	
AIDS in childhood	60	20 (40)§	30‖	10
Neonatal herpes	46	24 (63)	14	8
Reye's syndrome	80	35 (57)	26	19
Kawasaki disease	190	155 (86)	26	9
Haemolytic uraemic syndrome	98	74 (91)	7	17
Haemorrhagic shock encephalopathy syndrome	27	14 (74)	5	8
Subacute sclerosing panencephalitis	50	43 (86)	7	0
Lowe's syndrome	19	9 (64)	5	5

*Meets case criteria.
†Reporting error, duplicate, revised diagnosis
‡Still being followed up by the investigator at 7 April 1988
§Seventeen of these, as well as two cases known to the Communicable Disease Surveillance Centre before BPSU reporting began, were included in *HIV infection in the UK:2*. The three exclusions were. one Irish case; one information incomplete, one report received too late for inclusion
‖Includes 14 cases who are HIV positive (10 symptomatic) but who do not meet the case definition for AIDS

Irish Paediatric Association (IPA) members with the scheme, for which the Unit and the investigators are extremely grateful.

Workload of respondents

Sensitive to retaining this goodwill, the BPSU conducted an analysis of workload as measured by the number of cases (all conditions) reported by each respondent for the period July 1986 to September 1987.

About two thirds of respondents had reported no cases, so their BPSU time commitment was restricted to ticking 'nothing to report' on the monthly card (the success of the scheme of course depends on the nil returns). Two thirds of those who did report notified only one case. The highest number, eight cases, was reported by only one paediatrician. These figures suggest that most respondents were not excessively burdened by the BPSU

New conditions

The Unit will, however, continue to monitor workload and respondents' comments in 1988 because further reportable conditions have been added this year, including (for one year only) diabetes, which has engendered a relatively high rate of positive returns. The other new conditions are: haemorrhagic disease of the newborn; galactosaemia, drowning and near-miss drowning, rheumatic fever; and congenital rubella. The last two were retrospective studies each on the report card for one month only. Lowe's syndrome reporting was discontinued from April 1988 when that study was completed.

Response rate

The response rate (proportion of cards returned by 90 days after each mailing) rose steadily from an average of 81% for the first three mailings in 1986 to 90% for the last three in 1987. An average of over 90% for the whole period was achieved by respondents in 10 regions: seven in England, one in Scotland, and Northern Ireland, and Wales. The lowest rate, 77%, was from the Republic of Ireland.

Comment

The BPSU has progressed from the phase of being an experimental venture to that of consolidation. The operation is running smoothly with regular updating of the mailing list, monitoring of response rates and identification of, and contact with the few persistent non-respondents. A recent local effort to increase response rates from the Republic of Ireland has been most successful. The Unit has provided help and advice in the design of protocols and of proformas for data collection for which research workers have expressed appreciation. Several respondents have also commented on the value of the summary protocol cards as an educational aid and stimulus to heightened diagnostic awareness of these disorders.

All but one of the 12 spaces on the report card were filled by April 1988 and the Scientific Advisory Committee had continued to receive further applications. If accepted, these studies will be deferred until 1989 when space on the card will again be available. In view of the demand from research workers, measures to determine paediatricians' views on the optimum number of reportable conditions are currently in progress.

Funding of the BPSU for three years from 1989 has recently been secured by a generous donation from Children Nationwide. Thus the early promise of the Unit in facilitating research in rare childhood disorders continues to be realised. This success is entirely due to the enthusiasm and support of BPA and IPA members.

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Annotations

Special growth charts

The use of a reference chart for plotting sequential changes in height and weight is now a familiar routine for most health professionals involved in the care of children and increasingly for many parents as well. The idea of 'following a curve' is widely understood and a child who is 'falling off the chart' becomes the source of many an anxious consultation. In the Third World this idea has been exploited in a dramatic way by presenting the centile chart as a 'road to health'. There are many children in the United Kingdom, however, for whom the Tanner and Whitehouse charts are not necessarily ideal.[1]

A special problem exists for children who have an intrinsic growth disorder making the standard height and weight ('distance') charts inappropriate as reference material. Many of these conditions are so rare that to construct a growth chart of 'normal' growth would be a major, although not impossible, task. Others are so variable in their clinical expression that the population is insufficiently homogeneous for this kind of approach. There remain a number of conditions, however, where clinical management of individual children is greatly helped by appropriate reference growth charts.

Down's syndrome

The growth of children with Down's syndrome has now been systematically studied for more than 60 years. Three studies by Brousseau (1928), Benda (1949), and Øster (1953) were analysed by Roche and appeared to show an improvement in stature of about 1 SD over this time period.[2] All these studies, together with that by Rarick and Seefeldt,[3] were of institutionalised children who all showed considerably poorer growth than the home reared group studied by Cronk.[4] The recently published growth charts by Cronk *et al* undoubtedly provide the best reference data available.[5] The centile charts are sex specific and cover the periods 1 to 36 months and 2 to 18 years. Growth rates were slowest in infancy and again at adolescence compared with normal children. At birth lengths and weights are reduced by about 0·5 SDs but by 3 years are down by 2 SDs for length and 1·5 SDs for weight. This tendency to be overweight compared with normals continues throughout childhood. The adolescent growth spurt is also less and is mostly accounted for by reduced leg growth. Children with Down's syndrome who have congenital heart disease tend to be 1·5 to 2·0 cm shorter and about 1 kg lighter. In general, all children with Down's syndrome appear to show greater variation in growth rates than normal children, so they may not remain on the same centile [2 6] This may arise from the effects of congenital heart disease, recurrent infection, or chronic upper airways obstruction.

Turner's syndrome

Growth studies in Turner's syndrome are complicated by the fact that many patients will have had treatment with anabolic or sex steroids (and recently growth hormone) and that only about 65% of patients with Turner's syndrome have the chromosome constitution 45,XO. Ranke *et al* have analysed the growth data from 150 untreated children and could find no difference between cases with 45,XO and other karyotypes,[7] and this finding is supported by another study of the growth of 45,XO and 45,XO/46,XX subjects.[8] Children with Turner's syndrome show a reduction in birth weight and length of around 540 g and 2·8 cm respectively. Height velocity in the first three years is close to normal but from then on there is a progressive decline in height velocity up to the age of about 14 years. Although only a minority of patients with Turner's syndrome show any significant pubertal growth spurt, they continue growing for longer so height gain in the second decade is only a little below normal. The growth data of untreated girls from four European studies have been combined with some British data to produce a growth chart showing mean (2SD) compared with normal girls.[9]

Other sex chromosome abnormalities

The growth of boys with Klinefelter's syndrome (47,XXY) is the best documented of the other sex chromosome abnormalities. The mixed longitudinal study by Schibler *et al* gives individual growth data, the mean height curve, mean height velocities, and upper/lower segment ratios in 54 boys.[10] In the prepubertal period the mean height follows closely to the 75th centile of the standard chart and this increased height is due to increased leg growth from infancy. Similar findings are reported by others who have also noted a reduced head circumference.[11 12] Pubertal progression is slower but prolonged compared with controls. The Edinburgh cytogenetic study reported the growth of 14 boys with 47,XYY and found it similar to that of the boys with Klinefelter's syndrome, although the head circumferences did not differ from controls.[12] Girls with 47,XXX on the other hand appeared to have normal growth.

Skeletal dysplasias

A comprehensive study of height, height velocity, upper/lower segments, and head circumference in 403 individuals with classical achondroplasia has been published by Horton *et al*.[13] Height velocity rapidly declines during the first two years of life to reach and stay at about the third centile resulting in a progressive loss of height compared with normals. This is almost entirely due to growth failure in the lower segments in the first five years though subsequently growth of the trunk is subnormal as well, especially in girls. It was not possible in this study to assess the extent of the pubertal growth spurt. The head circumference charts are very useful for determining the onset of hydrocephalus, which may be difficult to diagnose in achondroplasia. The same group have also published growth curves for the rarer skeletal dysplasias including diastrophic dysplasia, spondyloepiphyseal dysplasia congenita, and pseudoachondroplasia.[14] These data are based on a limited number of observations from a small number of patients and so are presented as mean (SD).

Using special growth charts

Clinically the most useful form of reference growth chart is the centile chart While not all the data in these studies have been presented in this form, provided means and SDs are available for different ages, it is possible to construct similar growth curves using appropriate statistical smoothing techniques.[9] The cross sectional data that have been reported in most of these studies will usually be adequate for the prepubertal period though additional longitudinal data may be needed during puberty. Examples of the uses of these special growth charts include adult height prediction and assessing the effects of various forms of treatment in Turner's syndrome,[9] and the detection of growth failure in Down's syndrome. A novel approach to the use of special growth charts are the theoretical weight control charts constructed by Griffiths and Edwards for boys with Duchenne muscular dystrophy.[15] With disease progression and declining activity, muscle tends to be replaced by fat so that increased weight places an extra strain on already weakened muscles. Their charts have been designed as a guide to dieting. There is still a considerable need for improvement in presentation and accessibility of existing data and for further studies especially of growth velocities and of growth during puberty in many of these conditions.

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Adolescent outcome for hyperactive children

What happens to children who have been diagnosed as hyperactive when they reach adolescence? A number of studies involving North American populations have now attempted to provide an answer. Most of these were undertaken when the diagnosis of hyperactivity was defined by the *Diagnostic and statistical manual of mental disorders* (DSM II) as a disorder 'characterised by overactivity, restlessness, distractibility and poor attention span, especially in young children'.[1] This diagnosis accounted for about 5·5% of the general elementary school population,[2] and up to 30–40% of child clinic cases [3] Notably, the definition added that 'The behaviour usually diminishes in adolescence' This statement was controversial at the time and whether the hyperactive symptomatology disappeared or not, some felt that the disorder acts as a precursor to the development of social, personality, or even gross psychopathological disorders in adult life. With the arrival of DSM III and the conceptual change of hyperactive syndrome to attention deficit disorder, do we know the answer?

Outcome study methodology

Outcome studies of childhood hyperactivity are typically of two types: follow up and follow back.[4] The problem with the latter is that the subject pool is often untypical of the general population of hyperactive individuals as they are, for example, adult psychiatric patients or adults with continuing hyperactive behaviours. Of the follow up studies, many have failed to use control subjects, which makes it difficult to extrapolate the results to the general population of hyperactive children. Controlled, follow up studies are therefore likely to be the most reliable sources of information. If adolescence is arbitrarily defined as the age group 11–18, eight such studies qualify for inclusion in an analysis [5–12]

Drawing conclusions from even these studies is problematic because of the variability of study design. There is, for example, little consistency in the type of control subjects used (for example, sibling controls, supernormal controls) and the degree to which they are matched. If, for example, supernormal controls are used in which subjects have been selected for an absence of any behavioural or psychological disorder, this tends to exaggerate the difference in symptomatology between index and control subjects. Attrition rates, where reported, range upwards to 40% with only one of the studies exploring the difference between those subjects who were followed up and those who were lost to follow up.[12] Not having this information makes it difficult to assess the representativeness of the subjects studied compared with the original group identified for follow up.

Finally, the selection criteria for index subjects varies between studies. The DSM II diagnostic criteria lack precision but commendably all but one of the studies have defined in more detail the selection criteria used Even so there is variability, which makes it difficult to reliably combine information from different studies. Despite these drawbacks the studies under review do produce results that are consistent across studies

Results from the controlled, follow up studies

SYMPTOMATOLOGY

The study by Lambert *et al*[12] showed that the course of the disorder is variable between individuals [12] By 14 years of age, 20% of their sample were symptom free; 37% were not being treated by hyperactivity but had persistent problems of behaviour, learning, or emotion ('residuals'); and the remainder (43%), had emotional, learning, and behavioural problems and were still being treated for hyperactivity ('still hyperactive'). Gittleman *et al* diagnosed 40% of index subjects at follow up (mean age 18·3 years) as having some form of hyperactive disorder, with 48%, including those with hyperactivity, having a DSM III diagnosis of some type, but mainly in the conduct disorders range.[11] No case of major psychiatric illness was identified.

ANTISOCIAL BEHAVIOUR

There is evidence from four studies that some hyperactive children are at risk for developing antisocial behaviours in adolescence Hoy *et al* found that index subjects were more likely to have received a police caution than control subjects,[9] and Satterfield *et al*, using police records, found a higher incidence of arrests for index subjects in all socioeconomic groups compared with control subjets.[10] Lambert *et al* also found a significantly higher frequency of school suspensions and trouble with the police than was the case for control subjects.[12] In addition to finding a higher rate of school and non-school antisocial behaviours in index children, Gittleman *et al* also found a significantly higher rate of substance abuse disorders in index subjects in comparison with control subjects.[11]

COGNITION

Several studies have investigated the cognitive functioning of index and control subjects and overall it seems that many hyperactive children continue to have poorer styles of attentional performance and problem solving strategies. The studies of Cohen *et al*[7] and Lambert *et al*[12] found, using the Embedded Figures Test, that index subjects were significantly worse than control subjects in employing effective problem solving strategies. Poorer attentional test performances of index subjects were found in the studies of Hoy *et al*[9] and Lambert *et al*.[12]

ACADEMIC ACHIEVEMENT

Three studies reported that index subjects were more likely to have to repeat school grades than is the case of control subjects.[5,9,12] In addition, using more formal measures of educational attainment, Lambert *et al* found that index subjects scored significantly poorer on tests of mathematics and reading comprehension than did control subjects.[12] It is notable that the studies of Minde *et al*,[5] Gittleman *et al*,[11] and Lambert *et al*[12] all showed that index subjects scored significantly more poorly on tests of intelligence within a range of 7–11 points than did control subjects.

Discussion

The various studies reported on indicate that, compared with control subjects, adolescents who were hyperactive as children are more likely to continue to show hyperactive behaviours or other learning, emotional, and behavioural difficulties. Also they are more likely to be engaging in antisocial behaviours and those involving substance abuse. Cognitive difficulties, typically involving problem solving strategies and attentional performance, continue to be poor with related consequences on academic achievement.

What is noteworthy, however, is that the outcome is variable. Both the Gittleman *et al*[11] and Lambert *et al*[12] studies suggest that by early adolescence (about 14 years of age) up to 20% of index children are free of psychological or behavioural disorders, with the former study showing that by age 18 this number rises to 52%. Of the remainder, about 50% in each age group were still reported to be hyperactive and have associated problems, with the remaining 50% having problems of conduct and learning with a development towards antisocial and substance abuse behaviours by the time they reached late adolescence.[11] Broadly speaking then the outcome is tripartite and the interesting question is what determines the type of outcome?

The research tends to suggest that therapeutic intervention is not a significant outcome predictor. In all of the studies reviewed, index subjects received a variety of treatments, although in no study was this under full experimental control. In two studies reporting treatment data (Minde *et al*[5] and Lambert *et al*[12], 100% and 85% respectively of index subjects received stimulant medication, and in the case of the former study, outcome was found to be unrelated to the duration of drug taking. This finding is supported by a number of other studies that have failed to establish the efficacy of stimulant medication used for over a year.[13] In the Minde *et al*[5] and Lambert *et al*[12] studies subjects also received other types of treatment. In the latter study, for example, 57% had received special education or tutoring programmes, 19% psychological therapies, and 11% diet or motor treatment. Even so, the intervention efforts failed to improve the outcome for most subjects in their study, and Minde *et al* also failed to show any significant association between these other forms of treatment and outcome.[5]

Data from several studies suggest that those hyperactive children in adolescence who cease to have hyperactive symptoms but show other behavioural problems (residual type) are more likely to have shown higher levels of conduct disorder initially. This is true of the index children in the Weiss *et al*[6] study and in a further study by Satterfield and Schell.[14] In a more extensive study of outcome predictors in a group of hyperactive children, Paternite and Loney show that aggressive symptomatology is the largest outcome predictor with environmental and family variables also making a further but more modest contribution.[15]

There is little evidence to bring to bear on the question of what determines the differential outcome for those two other groups of children: one of which ceases to have psychological problems in adolescence and the other which continues to show hyperactive symptoms. There is, however, suggestive evidence that there may be a cognitive dimension on which these two groups differ. Lambert *et al* found that their 'no problem' group had the characteristic of being more cognitively mature compared with the 'still hyperactive' group.[12] Cognitive maturity is defined as a high score on measures of intelligence, formal reasoning, and academic achievement. It may be therefore, that a relatively superior cognitive ability may serve as a protective factor for the non-aggressive, hyperactive children particularly as it may ensure a better adjustment in the school environment. Conversely, some nonaggessive hyperactive children may be characterised by several types of cognitive deficits that persist into adolescence and continue to be associated with hyperactive symptomatology.

It will be profitable for future research studies to investigate further the features associated with the different outcomes for children diagnosed as hyperactive in childhood Cognitive ability may well be an important predictor but better measures will need to be developed of key variables such as attention, cognition, problem solving ability, and impulsivity. Finally, all of the studies here used normal control groups and it will be useful to explore how hyperactive children compared with other psychiatric groups. This will provide information about outcome characteristics which are specific to hyperactivity as opposed to those which accompany psychiatric and psychological disorders in general.

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Single photon emission computed tomography in seizure disorders

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SUMMARY Fourteen children with various seizure disorders were studied using a cerebral blood flow tracer, ^{123}I iodoamphetamine (0·05 mCi/kg), and single photon emission computed tomography (SPECT) In the five patients with radiological lesions, SPECT showed congruent or more extensive abnormalities. Five of the nine children with a normal scan on computed tomography had abnormal SPECT studies consisting of focal hypoperfusion, diffuse hemispheric hypoperfusion, multifocal and bilateral hypoperfusion, or focal hyperperfusion. A focal lesion seen on SPECT has been found in children with tonic-clonic seizures suggesting secondarily generalised seizures. Moreover the pattern seen on SPECT seemed to be related to the clinical status. An extensive impairment found on SPECT was associated with a poor evolution in terms of intellectual performance and seizure frequency. Conversely all children with a normal result on SPECT had less than two seizures per year and normal neurological and intellectual development.

The usefulness of studies with positron emission tomography in adult epilepsy is now well established.[1-3] Both cerebral metabolism and cerebral blood flow are significantly increased during focal or generalised seizures while both are depressed in the postictal and interictal state.[2,3] The presence of the interictal abnormality is remarkable in view of the fact that neuroradiological techniques usually fail to show any structural lesions in patients who might benefit from surgical treatment.[4]

Unfortunately, facilities for positron emission tomography are not widely available and remain very expensive. New cerebral blood flow tracers which are labelled with conventional γ ray emitters have been developed and allow the use of the single photon emission computed tomographic (SPECT) devices present in most nuclear medicine departments. The major determinants of the brain distribution of these tracers are cerebral blood flow and neuronal mass.[5] Although this technique is purely semiquantitative, its low cost and convenience make it highly attractive for a widespread clinical use.

Studies performed in adults using ^{123}I iodoamphetamine and SPECT have shown similar alterations as previously described in positron emission tomography.[6] Childhood epilepsy is a complex disorder, as indicated by the clinical pleiomorphism, the variety of aetiologic factors, and the unpredictable evolutions. There are only a few available data on abnormalities of cerebral metabolism in seizure disorders.[7,8] In this report we present our initial experience of cerebral blood flow imaging using ^{123}I iodoamphetamine and SPECT in children with various seizure disorders.

Patients and methods

Fourteen children aged 2 months to 16 years were investigated after informed consent of the parents and according to a protocol accepted by our local committee for medical ethics. Nine were known and treated epileptics: three had tonic-clonic seizures, two had complex partial seizures, two suffered from Bravais-Jacksonian crisis, one from absences, and one from a Lennox-Gastaut syndrome. All were investigated interictally, from three days to eight months after the last seizure. Four children were studied from 12 hours to five days after their first tonic-clonic seizures and were free from anticonvulsant treatment. One child was seen one week before the onset of tonic-clonic seizures. The reason for the examination was severe neurological hypotonia. Clinical data are presented in table 1.

High purity ^{123}I produced by the (p,5n) reaction was used to label the iodoamphetamine. Five children (patients 5, 10, 11, 13, 14) were given

Table 1 *Clinical data*

Patient No	*Age*	*Seizures*				*Treatment*	*Results of neurological and neuropsychological examination*
		Type	*Age of onset*	*Aetiology*	*Frequency*		
1	9 years	CPS	7 years	Cerebral birth injury	1-2/week	Carbamazepine	Right hemiparesia, school difficulties
2	11 years	TCS	4 years	Cerebral birth injury	1-2/year	Sodium valproate	Left hemiparesia
3	12 years	L-G	1 year	Unknown	2-3/month	Phenytoin, sodium valproate	Mentally retarded
4	13 years	TCS	13 years	Central nervous system demyelinating process	—	—	School difficulties
5	7 years	TCS	1 year	Tuberose sclerosis	2-3/month	Sodium valproate, nitrazepam	Mentally retarded
6	8 years	CPS	7 years	Unknown	3-4/week	Carbamazepine	Mentally retarded
7	16 years	B-J	1 year	Unknown	1-2/year	Sodium valproate	Normal
8	13 years	B-J	6 years	Unknown	1/year	Sodium valproate	Normal
9	12 years	TCS	4 years	Unknown	1-2/year	Sodium valproate	Normal
10	2 years	TCS	2 years	Febrile seizure	—	—	Normal
11	2 months	TCS	2 months	Unknown	—	—	Normal
12	13 years	TCS	13 years	Unknown	—	—	Normal
13	6 years	Absences	5 years	Unknown	1/month	Sodium valproate	School difficulties
14	4 months	TCS	4 months	Central nervous system heredodegenerative disease	—	—	Severe hypotonia

CPS=Complex partial seizures, TCS=Tonic-clonic seizures; B-J=Bravais-Jacksonian seizures; L-G=Lennox-Gastaut syndrome.

pentobarbitone (Nembutal, 5 mg/kg intrarectal) one hour before the examination. Patients were placed in a quiet environment, then an intravenous line was inserted into the forearm. About three minutes later 0·05 mCi/kg of ^{123}I iodoamphetamine were administered (with a minimum of 0·5 mCi) and after another 30 minutes children were taken to the camera room. Depending upon the child's size, either the head or the whole trunk was fixed in a polystyrene vacuum cushion. All the children were perfectly quiet throughout the examination. SPECT imaging was performed using an Elscint rotating camera and a low energy, high sensitivity collimator. Data for 360° were collected using 30 second frames and 6° increments. Transaxial and coronal reconstructions were calculated after a high frequency cut off using a Hamming-Hann filter by an Apex 415 computer system. The transverse axis was reorientated along the orbitomeatal line. Slices were 2 pixels thick (17 mm). After a background subtraction of 7% of the maximum, differences of more than 12% between symmetrical regions of the brain were considered significant. Computed tomography was performed in the same week with the Siemens Somatom DRH head scanner using a standard technique.

Results

The findings on electroencephalography, computed tomography, and SPECT are summarised in table 2. A normal SPECT pattern is displayed in the figure (A).

(1) PATIENTS WITH LESIONS ON COMPUTED TOMOGRAPHY (N=5)

Two children (patients 1 and 2) who had intractable complex partial seizures and rare tonic-clonic seizures, respectively, had a large sylvian porencephalic cyst: in both cases SPECT showed a congruent perfusion defect. Patient 3 suffered from Lennox-Gastaut syndrome and mental retardation; cerebral atrophy was seen on computed tomography and a SPECT pattern of multifocal cortical defects. Patient 4 presented with two inaugural consecutive tonic-clonic seizures. Both computed tomography and magnetic resonance imaging showed bilateral periventricular abnormalities, with the magnetic resonance imaging contrast suggesting demyelination. SPECT performed five days after the last seizure showed bilateral periventricular and left cortical hypoperfusion (figure (B)). Patient 5 who had tuberous sclerosis and mild periventricular calcifications shown on computed tomography, suffered from mental retardation and frequent tonic-clonic seizures. SPECT showed multiple cortical and subcortical areas of hypoperfusion.

(2) PATIENTS WITH NORMAL COMPUTED TOMOGRAPHY (N=9)

(a) With focus on electroencephalography

In patient 6 intractable complex partial seizures

Table 2 *Results of electroencephalography, computed tomography, and SPECT*

Patient No	*Electroencephalography*	*Computed tomography*	*Iodoamphetamine-SPECT*
1	Normal	Left sylvian porencephalic cyst	Left sylvian defect
2	Normal*	Right sylvian porencephalic cyst	Right sylvian defect
3	Bilateral slow spike-and-wave discharges	Cerebral atrophy	Multifocal cortical defects
4	Normal*	Bilateral periventricular hypodensities	Bilateral periventricular and left cortical hypoperfusion
5	Diffuse polyspike-and-wave	Periventricular calcifications	Multiple foci of hypoperfusion
6	Spikes at left temporal	Normal	Left temporal hypoperfusion
7	Normal	Normal	Normal
8	Normal	Normal	Normal
9	Normal*	Normal	Normal
10	Normal	Normal	Normal
11	Normal*	Normal	Extensive right hemispheric hypoperfusion
12	Normal*	Normal	Left temporal hypoperfusion
13	Diffuse polyspike-and-wave	Normal	Left parietal focus of hyperperfusion behind a hypoperfused area
14	Slow background	Normal	Bilateral foci of hypoperfusion

*Result at time of SPECT; previous electroencephalograms had shown diffuse polyspike-and-wave

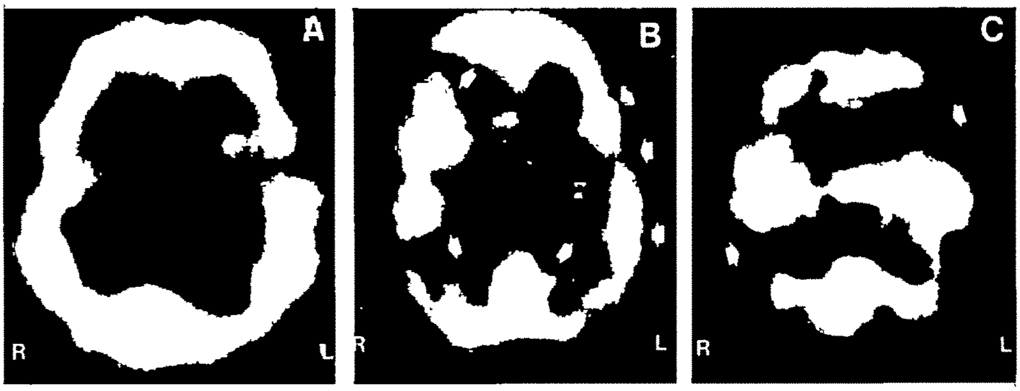

Figure Transaxial SPECT images in three children with seizure disorders Slice level is about 4 cm above the orbitomeatal line A=normal tomography (patient 7), B=bilateral periventricular and left cortical hypoperfusion (patient 4), C=left frontotemporal and right parieto-occipital areas of hypoperfusion (patient 14).

were attributed to a left temporal electroencephalographic focus. SPECT showed a focal abnormality consisting of a left temporal hypoperfusion.

(b) Without focus on electroencephalography
Patients 7 and 8 with rare Bravais-Jacksonian crisis, patient 9 with infrequent tonic-clonic seizures, and patient 10 who was studied four days after a first febrile tonic-clonic seizure, had normal electroencephalography and SPECT. Children 11 and 12 were seen, respectively, 12 hours and four days after a first tonic-clonic seizure when the electroencephalography was normal. SPECT showed an extensive right hemispheric hypoperfusion in patient 11 and a hypoperfusion limited to the left temporal lobe in patient 12. The electroencephalogram showed bilateral polyspike and wave in patient 13 who presented absences. Although the patient was asymptomatic at time of SPECT, there was an intense left parietal focus of increased uptake behind a hypoperfused area. Patient 14 had had severe neurological hypotonia since birth. Extensive examinations had failed to show any aetiology to that disorder, which is probably degenerative in nature. SPECT showed bilateral areas of hypoperfusion (figure (C)).

Discussion

In childhood epilepsy it is sometimes difficult to confirm the existence of structural lesions, to assess the indication for an anticonvulsant treatment, and to predict the evolution of the disease in terms of frequency of seizures and mental development. This is due to the complexity of the underlying neurological processes, as shown by the numerous clinical forms, patterns on electroencephalography, and aetiological factors, and to the relative paucity of information provided by conventional procedures: deep epileptic foci are frequently missed by routine electroencephalography,[9] and computed tomography often fails to show small gliotic areas or cytoarchitectural changes.[4] Moreover anatomic abnormalities seen on computed tomography or magnetic resonance imaging do not always correlate well with clinical or electroencephalographic data.[10]

The early work of Plum *et al* has show that haemodynamic and metabolic changes were coupled during convulsions.[11] Using positron emission tomography, several authors have described a similar pattern of cerebral metabolism and cerebral blood flow in seizure disorders.[2 3] The study of the perfusion alone can therefore be considered as a good approach to metabolic pertubations in epilepsy.

Recently introduced techniques combining SPECT and flow tracers have been proposed as a particularly versatile, convenient, and low cost alternative to cerebral flow studies using positron emission tomography. The first available molecules were amines labelled with ^{123}I—iodoamphetamine and hydroxy iodo propanediamine—and have been extensively used in a wide variety of disorders of the central nervous system. They are now superseded by ^{99m}Tc hexamethyl propylene amine oxime (HMPAO), which is superior for several reasons, in particular because of a lower cost and a lower absorbed radiation dose, allowing the administration of higher activities and leading to a better image quality. When we started this study, however, it was not commercially available in Belgium. The brain distribution of ^{123}I iodoamphetamine is in first approximation flow dependent, but little is known about the metabolism of this tracer during seizures, and other factors might interfere.[5 12] Data obtained using ^{123}I iodoamphetamine and SPECT in adult epilepsy, however, were consistent with findings from positron emission tomography.[5 6]

The use of SPECT in the study of children raises specific problems. Firstly, the effect of brain maturation on SPECT pattern is considerable. For obvious ethical reasons normal controls cannot be studied. Our experience, however, is in agreement with the evolution described in positron emission tomography and ^{18}F-2-fluoro-2-deoxy-D-glucose, where an adult like pattern is settled after 1 year of age (even though cerebral metabolism remains with much higher absolute levels of several years).[13] Secondly, because the patients have to be kept perfectly immobile sedation is often required, and one can argue about the use of medication in a functional neurological study. Nevertheless, it is unlikely that SPECT regional distribution could be significantly influenced by single and low doses of barbiturates.[14–16]

In the five patients with radiological lesions, SPECT showed congruent or more extensive abnormalities. On the other hand, five of the nine children with normal computed tomography had an abnormal SPECT study. Two patients with generalised seizures, diffuse polyspike-and-wave, and a normal computed tomogram had a focal or a regional SPECT hypoperfusion. This is in agreement with Podreka *et al* who have found, using SPECT and HMPAO, a high incidence (78%) of abnormally perfused regions in tonic-clonic seizures.[17] In patient 10 with absences and bilateral polyspike-and-wave, there was a hyperperfused focus. Interictal focal hyperperfusion has been described in patients suffering from complex partial seizures during spontaneous interictal bursts of focal electrical discharges and,[18 19] more recently, in a patient studied several hours after a tonic-clonic seizure in a state of psychomotor agitation, impaired consciousness, and with generalised paroxysms shown on electroencephalography.[17]

The ability of SPECT imaging to detect lesions not visualised by conventional procedures has potential diagnostic, therapeutic, and prognostic implications. The discovery of an interictal focus of hypoperfusion of hyperperfusion could help to assess the epileptogenic nature of ictal like phenomena. A focal abnormality in children with absences or tonic-clonic seizures could target the treatment towards focal epilepsy. In intractable seizures, surgical procedures could integrate the data from SPECT: limited resection or corpus callosotomy might be proposed in focal or diffuse hemispheric involvement. An extensive SPECT impairment is probably associated with a severe brain dysfunction and a poor clinical evolution in terms of intellectual performance and seizure frequency. Indeed, in our limited series the SPECT pattern was intimately related to the clinical status: school difficulties, mental retardation, frequent seizures, and neurological deficit were found in eight of 10 patients with abnormal SPECT, and conversely, all children with normal SPECT had less than two seizures per year and normal neurological and intellectual development.

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Randomised controlled trials of phenobarbitone and valproate in febrile convulsions

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SUMMARY Results from British trials of phenobarbitone and valproate for the prophylactic treatment of febrile convulsions were pooled and analysed on an intention to treat basis. The overall odds ratio for phenobarbitone was 0·8 and for valproate 1·42. Neither result was significant. Neither treatment can be recommended in the light of experience.

Controlled trials of drug treatment are usually pragmatic studies of treatment practice, and analysis should then be on an intention to treat basis. The question being asked is whether the intention to treat a population of children with febrile fits with anticonvulsants reduces the risk of recurrence relative to that in a control group. Many trials have excluded children from analysis who did not take their medication through either poor adherence to instructions or side effects. Analysis on this basis answers the question of whether risk of recurrence is reduced in quite a selected population which is difficult to define in advance.

Analysis on an intention to treat basis demands that children are analysed with the group to which they were originally allocated. Invariably some children are lost to follow up and available resources make this difficult to overcome. An assumption is usually made in the analysis that no bias has been introduced through this happening. Studies have shown apparently conflicting results. This is often due to small study groups either exaggerating or overlooking clinical benefit due to the play of chance. Pooled analysis leaves less to the play of chance by increasing the study population size. The method used is similar to that used in multicentre trials. Within centre differences between study and control groups become within study differences that are estimated and then pooled. An overall odds ratio (relative risk) is provided. This is the risk of recurrence in the treatment group relative to controls. An odds ratio of unity thus will signify no difference. An odds ratio of less than unity suggests some treatment benefit; greater than unity no benefit. When the odds ratio and its 95% confidence interval lie entirely to one side of unity the result is significant at $p<0·5$.

The method assumes data from all trials are available. None must be omitted because they showed negative results and were therefore unpublished. The method does not assume that one trial is directly comparable with another, but does assume the true odds ratio to be the same for each.

Method

Statistical analysis was identical to that used by Collins *et al.*[1] Six British trials of phenobarbitone[2 3 5–8] were identified and four of valproate [4 6–8] The table summarises data from the trials.

Trials were identified through a computerised literature search. Those unpublished were identified by writing to all members of the British Paediatric Neurology Association and paediatricians known to have participated in such work.

Children were reallocated to the groups to which they were originally assigned before reanalysis of data. Details were usually available from the paper itself or clarification was sought from the authors. Data in all but one paper can be confirmed.[7]

Results

The numbers in each trial and recurrences in each study group are summarised in the table. The pooled analysis of the phenobarbitone and valproate trials is summarised in the figure.

For phenobarbitone the odds ratio varied from 0·42[6] to 2·07[7]. in two it was less than unity and in four greater. The overall odds ratio for the 535 children was 0·8 (95% confidence interval: 0·53 to 1·20) a non-significant result Sixty six of the 296 (22%) treated children had recurrences compared with 58 of 236 (25%) controls.

Table *Characteristics of randomised controlled British trials of phenobarbitone or valproate, or both, in febrile convulsions*

Study (reference)	*Age on entry*	*Follow up period*	*No of patients followed up*		*No of recurrent febrile convulsions*	
			Treated	*Control*	*Treated*	*Control*
Phenobarbitone trials						
[2]	6 months–3 years	6 months	88	73	10	14
[3]	6 months–4 years	6 months	51	10	14	2
[5]	<24 months	12 months	50	45	10	15
[6]	6–18 months	Mean of 13 5 months	23	21	4	7
[7]	6–42 months	24 months	43	27	16	6
[8]	6–72 months	Mean of 30 months	41	60	12	14
Overall			296	236	66	58
Valproate trials						
[4]	6 months–6 years	12 months	30	28	8	9
[6]	6 months–6 years	Mean of 13 5 months	20	21	1	7
[7]	6 months–6 years	24 months	45	27	20	6
[8]	6 months–6 years	Mean of 30 months	50	60	20	14
Overall			145	136	49	36

Plasma drug concentrations were measured in each trial except that of Bacon *et al*[5] which measured salivary concentrations

With valproate the odds ratio varied from 0·11[6] to 2·8,[7] in two it was less than unity and in two greater The overall odds ratio was 1·42 (95% confidence interval: 0·85 to 2·36), also a non-significant result. Forty nine of 145 (34%) treated children had recurrences compared with 36 of 136 (26%) controls.

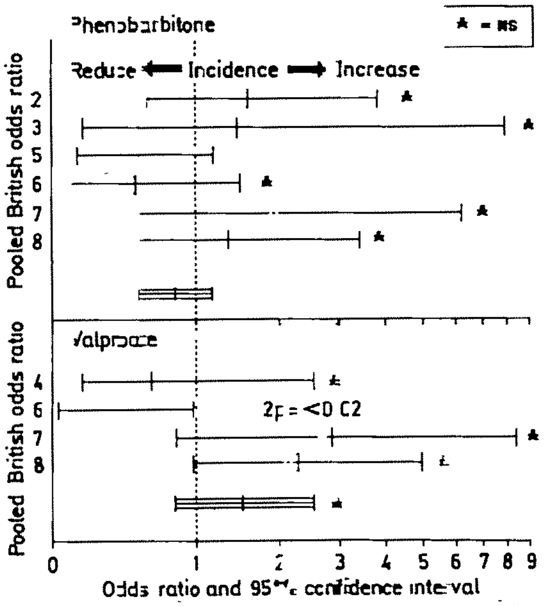

Figure *Pooled odds ratio of recurrent fit in randomised controlled trials of phenobarbitone and valproate with 95% confidence limits.*

Discussion

Only the British experience has been considered as the logistic problems in identifying unpublished trials showing negative results on a world basis seemed insurmountable. The analysis shows well how small study groups serve to exaggerate benefits or drawbacks of treatment. All the trials have been too small for paediatricians to use their findings with confidence.

Pooled analysis of the British experience fails to show any overall value in deciding to treat children who have febrile convulsions with anticonvulsants. The results do suggest that phenobarbitone might prevent as many as half the recurrences but they establish that any benefit from valproate is likely to be unacceptably small

The overall risk of recurrence is 26%. If the odds ratio of 0·8 for phenobarbitone trials were significant one would have to give anticoagulants to 100 children to stop five having a recurrence.

With side effects reported in up to 40% of the treated group it must be concluded that prophylactic treatment for febrile convulsions cannot be recommended. Alternative methods of treatment must be assessed such as the administration of rectal diazepam in those particularly at risk of recurrence. Meanwhile clear advice to parents on the first aid management of a seizure and how to gain access to medical care remain most important.

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Prognosis of partial epilepsy

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SUMMARY The prognosis of partial epilepsy in childhood (excluding cases of benign partial epilepsy) was studied; the average follow up period was 7·4 years. Improvement rate of seizure status was 82·3%. We studied favourable prognostic factors and found that those most often associated with seizure improvement were familial convulsions and idiopathic forms, no generalised seizures before partial onset, low frequency of seizures after 12 months of treatment, short duration of epilepsy, and no background activity abnormalities on electroencephalography. We also observed such factors as mental retardation, neurological abnormalities, and behaviour and cognitive disorders. Factors that determined the prognosis for social adjustment were similar to those for seizure improvement. We discuss the favourable prognosis of partial seizures in childhood and the predictive factors.

Partial epileptic seizures in childhood are quite common representing, according to various authors, from 40%[1,2] to 70%[3,4] of the whole range of epileptic forms found among children. The literature on partial epileptic seizures has focused upon the electroclinical characteristics of the single forms, particularly those with complex symptomatology[5-8] and on the efficiency and the side effects of antiepileptic treatment.[9-11] There appear to be few studies, however, on the prognosis of this syndrome in children.

The past pervasive tendency to consider the prognosis for partial seizures as much less favourable than that for generalised seizures has now been re-examined. Favourable outcomes of seizure symptomatology in childhood have been seen in at least two thirds of such patients.[4,12,13] There is favourable prognosis for social adjustment and intellectual development as well. Some authors found that one third or fewer patients had difficulties in social adjustment, whether or not they were associated with mental retardation.[4,6,14] In this study we have given special regard to the evolution of seizure symptomatology and to associated disturbances (that is, mental retardation, neurological abnormalities, behaviour and cognitive disorders) which compromise or hinder social adjustment. Furthermore we tried to establish which initial electroclinical characteristics and which course patterns have the greatest influence on seizure outcome, in order to define possible predictive factors for patients with this type of seizures.

Patients and methods

We studied 261 consecutive patients (136 males and 125 females) with partial epilepsy, who presented with seizures, on at least two separate occasions, that were not symptomatic of acute cerebral alterations of a febrile, toxic, or metabolic nature. The age of appearance of partial seizures ranged from 10 months to 13 years (average age 4·9 years). We excluded all patients with benign partial epilepsy[15] or with partial epilepsy constantly associated with generalised seizures. The average duration of the follow up period was 7·4 years. All the patients were having antiepileptic treatment, and the blood concentrations were periodically reviewed, all the patients underwent at least semiannual clinical and electroencephalographic examinations (in waking and sleeping conditions). Eighty nine patients presented with partial seizures with elementary symptomatology; 109 with partial seizures with complex symptomatology; and 63 with partial seizures secondarily generalised. Aetiological prenatal, perinatal, or postnatal factors were present in 112 cases: 62 patients had birth injuries, 31 head traumas, and 19 infectious pathologies of the central nervous system with contemporary or subsequent onset of partial seizures.

We divided the whole sample into two main groups according to seizure outcome at the fifth follow up year.[1] Improved cases included patients whose frequency of seizures was reduced by at least two thirds of the first year frequency and patients who presented stable remission of convulsive symptomatology for at least two years.[2] Patients who were worse had an unchanged or a higher seizure frequency than at onset or had a seizure frequency not less than monthly.

We studied neurological and mental evolution in relation to the constant and stable presence of mental retardation of various levels (IQ <80), permanent neurological abnormalities (hemiplegia, tetraplegia, etc), behaviour disorders considerably affecting social adjustment (for example, childhood hyperkinesia, uncontrolled aggressiveness, etc), and cognitive disorders in absence of mental retardation (for example, speech and learning disabilities).

We observed the evolution of the electroencephalographic tracings in relation to the initial focal location; to possible regional, contralateral, or intrahemispheric migration; and to normalisation.

We investigated factors predictive of seizure outcome and of neurologic and mental evolution by correlating the trend of convulsive symptomatology at the end of the observation and the neurological and mental abnormalities, and behaviour and cognitive disorders, with the following initial and course characteristics: type of partial seizures, aetiology and/or positive family history of convulsions and/or epilepsy in first and/or second degree relatives, predating generalised seizures and febrile convulsions, age at partial seizure onset, initial seizure frequency, initial patterns on electroencephalography, frequency of seizures after 12 months treatment, duration of epilepsy (that is, the period between the first and the last partial seizure), and stable and persisting abnormalities in background activity on electroencephalography (such as diffuse stable delta activity).

Finally, we correlated seizure outcome with the patients' neurological, mental, and electroencephalographic results. We used the χ^2 test for comparison of percentages, resorting to the Yates's correction factor when more than 20% of the observed numbers was equal to or lower than 5 Differences in p values equal to or lower than 0·05 were considered significant.

Results

(1) SEIZURE OUTCOME AT THE END OF THE FOLLOW UP PERIOD

At the end of the observation period, 153 patients had been free from seizures for at least two years; 61 had an improvement of initial seizure frequency; 36 had an unchanged seizure frequency; and 11 had a higher seizure frequency compared with that at onset.

(2) EVOLUTION OF ELECTROENCEPHALOGRAPHIC TRACINGS AT THE END OF THE FOLLOW UP PERIOD (TABLE 1)

In 109 patients the electroencephalographic tracings had become normal, 140 had focal specific abnormalities, and 12 had multifocal specific abnormalities.

During the follow up period transient multifocal activity was seen in 20 patients; this activity was then replaced by migrating focal activity. Of the whole sample, 83 patients presented subsequent migration of the electroencephalographic focus and 31 of them had normal tracings at the end of the follow up. Among the patients without subsequent migration of the initial focus (178) electroencephalography became normal in 77. In most cases the initial locations of foci, subsequently normalised, were parietal, occipital, and frontal. The percentage becoming normal was very low, however, in subjects with focal initial location in the temporal area, both in the case of subsequently migrating foci (12/45, 27%) and of foci stable in time (29/76, 38%). The rate that the tracings became normal did not differ in the two groups (constant foci and migrating foci) either in relation to the total number of cases or to single initial location of foci on electroencephalography.

Table 1 *Location of initial foci, migration, and normalisation*

Location	*Initial foci*		*Migration*		*No migration*	
	Total No	*Normalisation No (%)*	*Total No (%)*	*Normalisation No (%)*	*Total No (%)*	*Normalisation No (%)*
Frontal	45	18 (40)	18 (40)	6 (33)	27 (60)	12 (44)
Parietal	30	15 (50)	6 (20)	5 (83)	24 (80)	10 (42)
Occipital	28	16 (57)	8 (28)	5 (62)	20 (72)	11 (55)
Temporal	121	41 (34)	45 (37)	12 (27)	76 (63)	29 (38)
Hemispheric	31	18 (58)	6 (19)	3 (50)	25 (81)	15 (60)
Multifocal	6	1 (17)	—	—	6 (100)	1 (17)
Total	261	109	83	31	178	78

(3) FACTORS INFLUENCING SEIZURE OUTCOME AND NEUROMENTAL EVOLUTION (PREDICTIVE FACTORS)

Data resulting from comparison of initial and course characteristics and final outcome of seizures are shown in table 2. No significance was achieved for febrile convulsions predating partial onset, seizure initial frequency, and the initial pattern on electroencephalography. With regard to neuromental evolution at the end of the follow up period 130 patients had at least one of the following disturbances: 44 patients had mental retardation, 49 neurological abnormalities, 45 behaviour disorders, and 43 cognitive disorders

When we compared characteristics found initially and during the follow up period with mental retardation we found the following associations. (1) Type of seizure: partial seizures with elementary symptomatology, mental retardation was found in 17/89 patients (19%); partial seizures with complex symptomatology, 24/109 (22%); and partial seizures secondarily generalised, 3/63 (5%) (p<0 025). (2) Aetiology: ascertained aetiology, 17/70 patients (24%); ascertained aetiology plus a positive family history, 13/42 (31%); positive family history, 5/59 (8%); and idiopathic forms, 9/90 (10%) (p<0·005). (3) Age at seizure onset: 0–4 years, 29/118 patients (25%) and 4–12 years, 15/143 (11%) (p<0·01). (4) Frequency of seizures after 12 months' treatment: high, 21/51 patients (41%); medium, 9/60 (15%); and low, 14/150 (9%) (p<0·0005). (5) Duration of epilepsy: two to four years, 16/147 patients (11%) and four to 13 years, 28/114 (25%) (p<0·005). (6) Background activity on electroencephalography: present, 15/30 patients (50%) and absent, 29/231 (13%) (p<0·0005). No differences were found for the initial frequency of seizures.

When we compared the characteristic found with neurological abnormalities we found the following associations. (1) Type of seizure: partial seizures with elementary symptomatology, neurological abnormalities were found in 24/89 patients (27%); partial seizures with complex symptomatology, 29/109 (20%); and partial seizures secondarily generalised, 3/63 (5%) (p<0·005). (2) Aetiology: ascertained aetiology, 24/70 patients (34%); ascertained aetiology plus positive family history, 11/42 (26%); positive family history, 6/59 (10%), and idiopathic forms, 8/90 (9%) (p<0·005). (3) Age at seizure onset: 0–4 years, 33/118 patients (28%) and 4–12 years, 16/143 (11%) (p<0·001). (4) Frequency of

Table 2 *Initial and course characteristics compared with seizure outcome**

	Total No	*No (%) who improved (n=214)*	*No (%) who worsened (n=47)*	*p Value*
Type of seizure:				
Partial elementary	89	71 (80)	18 (20)	NS
Partial complex	109	85 (78)	24 (22)	
Partial secondarily generalised†	63	58 (92)	5 (8)	
Aetiology:				
Ascertained aetiology	70	50 (72)	20 (29)	0·001
Ascertained aetiology + positive family history	42	29 (69)	13 (31)	
Positive family history	59	53 (90)	6 (10)	
Idiopathic forms	90	82 (91)	8 (9)	
Generalised seizures predating partial onset				
Present	23	9 (39)	14 (61)	0·0005
Absent	238	205 (86)	33 (14)	
Age at onset				
0–4 years	118	89 (75)	29 (25)	0·025
4–12 years	143	125 (87)	18 (13)	
Frequency of seizures after 12 months treatment‡				
High	51	27 (53)	24 (47)	0·005
Medium	60	49 (81)	11 (19)	
Low	150	138 (92)	12 (8)	
Duration of epilepsy				
2–4 years	147	136 (93)	11 (8)	0·0005
4–13 years	114	78 (68)	36 (32)	
Background activity on electroencephalography:				
Present	30	20 (67)	10 (33)	0·025
Absent	231	194 (84)	37 (16)	

*No significances were achieved for febrile convulsions predating partial onset, seizure initial frequency, and initial pattern on electroencephalography.

†Partial secondarily generalised v partial elementary + partial complex, p=0·02

‡High=multidaily, daily, or weekly medium=fortnightly, monthly, or quarterly, and low=six monthly or yearly

seizures after 12 months' treatment: high, 16/51 patients (31%); medium, 9/60 (15%); and low, 24/150 (16%) ($p<0\cdot05$). (5) Duration of epilepsy: two to four years, 21/147 patients (14%) and four to 13 years, 28/114 (25%) ($p<0\cdot05$). (6) Background activity on electroencephalography: present, 15/30 patients (50%) and absent, 34/231 (15%) ($p<0\cdot005$). No differences were found for the initial frequency of seizures.

When we compared the characteristics found with behaviour disorders we found the following associations. (1) Type of seizure: partial seizures with elementary symptomatology, behaviour disorders were found in 16/89 patients (18%); partial seizures with complex symptomatology, 26/109 (24%); and partial seizures secondarily generalised 3/63 (5%) ($p<0\cdot01$). (2) Aetiology: ascertained aetiology, 17/70 patients (24%); ascertained aetiology plus a positive family history, 12/42 (29%); positive family history, 6/59 (10%); and idiopathic forms, 10/90 (11%) ($p<0\cdot025$). (3) Frequency of seizures after 12 months' treatment: high, 15/51 patients (29%); medium, 10/60 (17%); and low, 20/150 (13%) ($p<0\cdot05$). (4) Duration of epilepsy: two to four years, 13/147 patients (9%) and four to 13 years, 32/114 (28%) ($p<0\cdot005$). (5) Background activity on electroencephalography: present, 10/30 patients (33%) and absent, 35/231 (15%) ($p<0\cdot025$). No differences were found for the age at seizure onset and for the initial frequency of seizures

When we compared the characteristics found with cognitive disorders, the only significant association was in the type of seizure, with partial seizures with elementary symptomatology (18/89, 20%) and partial seizures with complex symptomatology (21/109, 19%) having a greater association than partial seizures secondarily generalised (4/63, 6%) ($p<0\cdot05$).

(4) PARALLEL COMPARISON OF SEIZURE OUTCOME, NEUROLOGICAL AND MENTAL STATE, AND THE OUTCOME OF ELECTROENCEPHALOGRAPHIC TRACING

Data are shown in table 3. No significant difference was found when we compared seizure outcome with neurological abnormalities, with foci migration shown on electroencephalography, and with the location of the initial foci shown on electroencephalography.

Discussion

In this series the outcome of patients with partial seizures was encouraging, remission of seizures for at least two years occurred in 59%. On the total sample, 17% had mental retardation, 19% had neurological abnormalities, and 17% had behaviour disorders. These data match the observations reported by other authors.[4, 12]

The results on electroencephalography and the clinical course tended to parallel each other,

Table 3 *Comparison of seizure outcome, neurological and mental state, and outcome of electroencephalographic tracing**

	Total No	*No (%) who improved*	*No (%) who worsened*	*p Value*
	Seizure and neurological and mental state outcome			
Mental retardation:				
Present	44	26 (59)	18 (41)	0·0005
Absent	217	188 (87)	29 (13)	
Behaviour disorders				
Present	45	29 (64)	16 (36)	0·001
Absent	216	185 (88)	31 (14)	
Cognitive disorders:				
Present	43	25 (58)	18 (42)	0 0005
Absent	218	189 (87)	29 (13)	
	Seizure and outcome of electroencephalographic tracing			
Final patterns				
Normal	109	105 (96)	4 (4)	
Focal abnormalities	140	105 (75)	35 (25)	0·0005
Multifocal abnormalities	12	4 (33)	8 (67)	
Migrating foci:				
Normalised	31	30 (97)	1 (3)	0·02
No normalised	52	39 (75)	13 (25)	
No migrating foci				
Normalised	77	73 (95)	4 (5)	0·0005
No normalised	101	72 (71)	29 (29)	

*No significances were found for comparison of seizure outcome with neurologic abnormalities, with foci migration seen on electroencephalography, and with location of initial foci seen on electroencephalography although the percentage of improvement in convulsive symptomatology exceeded the values of the normalisation of the electroencephalographic tracing. This finding is particularly stressed in other studies on partial seizures.[4,12,14]

The temporal area was the most frequent location of focus shown on electroencephalography in accordance with Scarpa.[12] Patients with the focus in this area also presented the lowest value of normalisation on electroencephalography, such as that found in patients with multifocal tracings. Migration frequency of foci with initial temporal location did not differ from migration frequency of foci in the other locations, although the normalisation percentage was much lower. Patients with temporal foci that did not migrate had the lowest value of normalisation; however, a less favourable trend of convulsive symptomatology did not correlate with these values.

Focal migration was not, by itself, associated with tracing normalisation at the end of the follow up period, nor with improvement of convulsive symptomatology. Kitagawa has noted that temporal, multifocal, and migrating tracings tend to less favourable evolution.[16]

As for predictive factors of seizure outcome, we found that an ascertained aetiology led to unfavourable seizure outcome. The presence of both a positive family history and ascertained aetiology, however, led to poor outcome. It is possible that the addition of brain insults to the genetic disposition to convulsions is responsible for the increase and the persistence in time of a convulsive tendency. On the contrary, the absence of ascertained aetiology, and the presence of a positive family history were often associated with definitely favourable outcome, as other authors have found.[6,12,13]

Poor control of seizures despite the introduction of antiepileptic treatment, was a very important factor in the subsequent evolution, whereas initial seizure frequency did not seem to influence prognosis. Other authors differ in their observation of this.[14]

A normal initial tracing on electroencephalography had no prognostic value: in fact, in our sample, all the patients presenting normal initial tracings subsequently presented focal activity. The persistence of stable abnormalities in background activity on electroencephalography was an unfavourable influence on seizure outcome. This finding has already been reported in other studies on the prognosis of epilepsy and is thus confirmed as well in partial seizures of childhood.[17,18] Factors predictive of unfavourable seizure outcome were: early onset, presence of generalised seizures predating partial seizure onset, and long duration of epilepsy.

We found a more favourable seizure outcome for partial seizures secondarily generalised compared with partial seizures with elementary symptomatology and partial seizures with complex symptomatology. Some authors report a more favourable outcome for complex seizures,[6,18] and others agree with our results for partial generalised ones.[14,16] We think that the presence of significant differences in the group with partial seizures secondarily generalised compared with the two other groups in our sample is due to the coexistence, in the groups with partial seizures with either elementary or complex symptomatology, of other types of partial seizures. In fact, it is well known that a stable association of various types of partial seizures is responsible, by itself, for a less favourable outcome.[14,19]

Predictive factors associated with unfavourable seizure trends were also associated with neurological abnormalities, mental retardation, and behaviour disorders. In many cases, patients with unfavourable seizure outcome were those presenting with an association of the above mentioned disorders. In our sample mental retardation and neurological abnormalities were less frequent than usual (17% and 19% respectively), and they were evident before the onset of partial seizures. They were associated, but not causally related, with unfavourable seizure trends; this probably depends upon the amount of basic brain involvement, in accordance with the finding of Sofijanov.[4] The low incidence of mental retardation and neurological abnormalities, and the lack of a causal relation between partial seizures and these pathologies, give evidence of the relative benignity of partial seizures in childhood.

There was no significant association between the presence of cognitive disorders and the characteristics found initially and throughout the follow up period. Speech and learning disabilities existed independently of characteristics linked with epileptic state. The percentage of cognitive disorders in our sample was similar to that in the general population. The outcome of partial seizures (even when benign epilepsies nosographically recognised are excluded) seems to be more favourable in childhood than among adults. We suggest that there exists a higher frequency of benign partial seizures among children, especially if they bear 'lesional' characteristics, than has previously been recognised.[3,20]

In conclusion, the main factors affecting a favourable prognosis are the following: (a) a family history positive for convulsions and the lack of ascertained aetiology; (b) absence of generalised seizures predating partial onset; (c) low seizure frequency after 12 months' treatment; (d) short duration of epilepsy; (e) absence of background activity abnormalities on electroencephalography; and (f) absence of mental retardation, neurological abnormalities, or behaviour disorders. The following factors seem to have no determining influence on the prognosis: (a) presence of febrile convulsions predating partial onset—age at onset; (b) initial seizure frequency; (c) initial tracings on electroencephalography; and (d) presence of cognitive disorders.

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Plasma testosterone in preterm infants with cryptorchidism

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SUMMARY Cryptorchidism is common in infants born preterm, yet the mechanism for its occurrence is still debated. In a study of 21 premature babies with cryptorchidism at 18 months post-term and 21 case matched controls, cryptorchid preterm infants failed to show the normal rise in plasma testosterone in the first postnatal week. This rise is thought to relate to residual maternal human chorionic gonadotrophin in the neonatal circulation. Infants with cryptorchidism also failed to show the later testosterone surge in the second month which has been related to endogenous gonadotrophin release. We speculate that inadequate stimulation of testosterone release by human chorionic gonadotrophin in the fetus might contribute to the pathogenesis of cryptorchidism in preterm infants. Our findings have implications for the medical treatment or possible prophylaxis of undescended testes in premature babies.

Cryptorchidism has received considerable scientific attention, yet its aetiology is still debated. Substantial evidence supports the view that there is an underlying disturbance of testosterone and gonadotrophin secretion in this condition.[1-4] In normal term and preterm infants high concentrations of plasma testosterone, close to adult values, are found during the first postnatal week, in association with residual human chorionic gonadotrophin in the neonatal circulation.[5 6] Subsequently, plasma testosterone concentrations fall, only to rise again in the second month under the influence of an endogenous surge in luteinising hormone.[5-7] In cryptorchidism this later surge in both luteinising hormone and testosterone is diminished.[1 2] Moreover, there is evidence that from infancy to puberty, children with undescended testes have reduced luteinising hormone responsiveness to luteinising hormone releasing hormone and reduced testosterone responsiveness to human chorionic gonadotrophin.[8 9]

Previous endocrinological studies on cryptorchidism have focused primarily on infants born at full term. We have reported a very high incidence of cryptorchidism in premature babies at 18 months' corrected age, reaching 19% in infants of less than 1000 g birth weight.[10] The aetiology of cryptorchidism in this special, high risk group has received little attention. In this study we have investigated plasma testosterone concentrations during the first three months postpartum in 21 preterm infants with cryptorchidism and in 21 case matched controls.

Subjects and methods

The study population included 21 babies born preterm, at a mean (SE) gestation of 30 (0·4) weeks, who were found to have cryptorchidism at 18 months' corrected age. Clinical details of these infants have been described.[10] Ten subjects had bilateral and 11 subjects unilateral cryptorchidism. Venous blood samples from these infants were available until they were discharged from hospital, at a median age of 40 days (range 17–90). Samples were taken at mean postnatal ages of 2 and 5 days, and then weekly until discharge.

A further group of 21 control infants were studied, each of whom had been matched carefully with an index case for (in order of priority) gestation, birth weight, duration of ventilatory assistance and, in view of the evidence that phototherapy may induce gonadotrophin release,[11] the cases were matched also for duration of phototherapy.

Venous plasma samples were collected, without haemolysis, into cooled heparinised tubes, centrifuged at 4°C, frozen within 30 minutes of sampling, and stored at −20°C. Plasma testosterone concentration was measured in duplicate 60 μl samples, by radio immunoassay after extraction into diethyl ether using the method described by Wheeler and Luther.[12] The sensitivity of the assay was 0·1 nmol/l. The antiserum cross reacted with dihydrotestosterone (20%), but had negligible cross reactions with androstenediol, androstenedione, oestradiol, progesterone, and cortisol.

Statistical analyses were performed using Student's *t* test and, when data sets were highly skewed, the Mann-Whitney rank sum test.

Results

Mean gestation, birth weight, days of mechanical ventilation required, and days of phototherapy were compared in index cases and controls, who were closely matched for these factors; the results are shown in the table.

The figure shows plasma testosterone concentrations in index cases and controls at mean ages of 2 and 5 days, weekly from week two to six and beyond week six (mean age 67 days; maximum 85 days) As samples were not always available at all periods for each subject unpaired *t* tests (or rank sum tests) were used for statistical comparisons. The decrease in sample numbers beyond week five resulted from discharge of some subjects from hospital. In the last period, six subjects in each group remained in the study and the testosterone value for each subject was the mean for samples taken beyond week six.

Table *Mean (SE) birth weight, gestation, days of mechanical ventilation, and days of phototherapy in 21 preterm infants with cryptorchidism diagnosed at 18 months' corrected age, and in 21 case matched case controls without cryptorchidism*

	Index cases (n=21)	*Controls (n=21)*
Birth weight (g)	1318 (56)	1339 (56)
Gestation (weeks)	30 (0 4)	30 (0·3)
Ventilation (days)	4 (1)	4 (1)
Phototherapy (days)	3 (0 5)	4 (0 7)

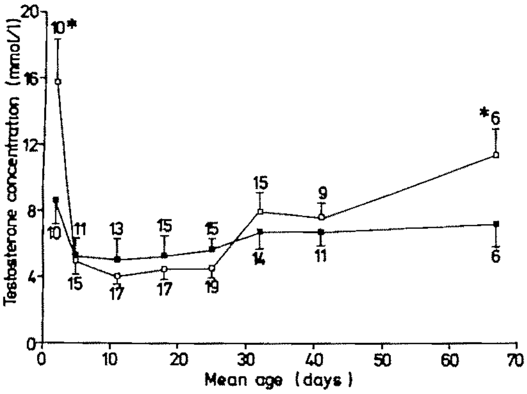

Figure *Plasma testosterone concentrations in preterm infants with cryptorchidism diagnosed at 18 months' post-term (closed squares) and in case matched infants without cryptorchidism (open squares) at eight periods during the first three months postpartum Asterisk indicates significant differences between index cases and controls*

At 2 days, index cases had significantly lower mean (SE) concentrations of plasma testosterone than controls: 8·6 (1·5) compared with 15·7 (2·6) nmol/l, p<0·01. In the controls a nadir in plasma testosterone concentration had been achieved by 11 days with a highly significant fall in testosterone values to 4·0 (0·4) nmol/l, p<0·001. In contrast, the fall in plasma testosterone in the index cases over this period to 5·0 (1·2) nmol/l did not reach significance. In the controls, plasma testosterone concentrations rose from the 11 day value to 8·0 (1·1) nmol/l in week five (p<0·001) and to 11·4 (1·5) nmol/l beyond week six (p<0·001). The index cases, however, showed no significant rise in plasma testosterone concentration during this period. Beyond six weeks, the difference in values between index cases and controls—11·4 (1·5) compared with 7·1 (1·3)—reached significance (p<0·05).

No relationship was found between plasma testosterone concentrations and the duration of phototherapy in any of the postnatal groups studied.

Discussion

We have shown that preterm infants in whom cryptorchidism was diagnosed at 18 months post-term failed to develop the normal testosterone surge in the second postnatal month. Thus preterm infants with undescended testes appear to be similar in this respect to full term infants with this condition.[1 2] There have been no previous reports, however, in either term or preterm infants with cryptorchidism, on plasma testosterone concentrations in the period immediately postpartum. We observed that preterm infants with this condition showed no primary rise of plasma testosterone, normally seen in both term and preterm infants early in the first week after birth,[5] and indeed seen in the case matched controls in this study.

We have observed that, below 32 weeks' gestation, there is an abrupt rise in the incidence of undescended testes.[10] These data raised the question of whether the aetiology of cryptorchidism in preterm infants differed from that in infants born at term. Our data suggest, however, that a diminution of testosterone release is a consistent feature in cryptorchidism, even if it occurs in the preterm infant. It might be supposed that such reduced testosterone secretion reflected a more general immaturity of the Leydig cells or the hypothalamus-pituitary-gonadal axis in babies born preterm. Yet our matched controls showed an early rise in plasma testosterone concentration, and Forest and others have shown that the surge in testosterone seen in the second month is normally higher in preterm than in term, male infants without undescended testes.[5] We have considered the possibility that cryptorchidism, at least in premature babies, may not be due to a primary endocrine defect in the infant but to a lack of a stimulatory influence that should have occurred in utero. Our data obtained on the second day postpartum are relevant in this respect; the relatively low concentrations of plasma testosterone immediately after birth in babies with cryptorchidism could imply that inadequate release of testosterone induced by maternal chorionic gonadotrophin in utero was the initial endocrine lesion. Further study is required on perinatal endocrine interrelations in premature babies to explore this hypothesis.

A number of investigators have advocated medical treatment for cryptorchidism, though the efficacy of this approach is debated.[13 14] Gonadotrophin and testosterone have been implicated in testicular descent and, on this basis treatment with luteinising hormone releasing hormone has been used with varying success.[13-16] Systemic testosterone alone results in testicular descent in primates,[17] and human chorionic gonadotrophin has been used successfully in cryptorchidism in man.[18] We suggest that the high incidence of undescended testes in preterm babies, and our findings that their primary and secondary rise in testosterone are diminished, would make it logical to explore endocrine treatment or prophylaxis in this special group.

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Low plasma triiodothyronine concentrations and outcome in preterm infants

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SUMMARY A major association has been found between low plasma triiodothyronine concentrations in preterm neonates and their later developmental outcome. Plasma triiodothyronine concentration was measured longitudinally in 280 preterm infants below 1850 g birth weight. Babies whose lowest recorded concentration was <0·3 nmol/l had, at 18 months' corrected age, 8·3 and 7·4 point disadvantages in Bayley mental and motor scales and a 8·6 point disadvantage on the academic scale of Developmental Profile II, even after adjusting for a range of antenatal and neonatal factors known to influence later development. Low concentrations of triiodothyronine were strongly associated with infant mortality, but not after adjusting for the presence of respiratory illness. There was no association between plasma triiodothyronine concentrations and somatic growth up to 18 months, and no association with necrotising enterocolitis or later cerebral palsy. Data on postnatal changes in plasma triiodothyronine concentrations are presented for reference purposes. While cited reference ranges for plasma triiodothyronine concentration appear suitable for well infants above 1500 g birth weight, smaller or ill babies often have very low values for many weeks. Our data are relevant to the debate on endocrine 'replacement' treatment in premature babies.

Triiodothyronine has about three to four times the metabolic potency of thyroxine and is formed by monodeiodination of thyroxine in tissues. Fetal tissues seem incapable of this step until relatively late in gestation[1]; hence plasma triiodothyronine concentration is very low in the human fetus before 30 weeks' gestation.[2–4] A number of investigators have shown that plasma triiodothyronine concentrations rise postnatally in infants born preterm, but in the early postpartum period values are below the normal range for full term infants and adults.[5–8] In some studies plasma triiodothyronine and thyroxine concentrations have been even lower in neonates with respiratory disease,[9 10] suggesting that, as in adult 'euthyroid sick syndrome',[11] severe systemic illness may depress thyroid function further.

Thyroid hormones play a critical part in the normal development of the lung,[12–14] gut,[15] and brain[16–18]; and the possibility that 'replacement' treatment in preterm infants could have favourable effects both in the short and longer term has been investigated by several groups.[19–21] It has been difficult to establish, however, that low plasma concentrations of thyroid hormones, in this special circumstance, reflect a deficiency state. Schonberger *et al* report a reduction in mortality rates of preterm infants given triiodothyronine and thyroxine in the neonatal period.[20] In other studies, no outcome advantages have emerged, for instance, in early growth or later development.[19 21]

In this follow up study, we have related plasma triiodothyronine concentration, measured longitudinally in 280 preterm infants, to growth, major morbidity, mortality, and neurodevelopmental outcome to 18 months' post term.

Patients and methods

A total of 280 infants, birth weights under 1850 g, were studied. Mean (SE) birth weight was 1330 (18) g and gestation 30·3 (0·2) weeks. These infants had been enrolled in a larger preterm infant feeding trial for which extensive data were collected on antenatal, perinatal, and postnatal factors.[22]

Plasma triiodothyronine concentrations were assayed on plasma samples taken while the infants were in the special care baby unit in Cambridge, Ipswich, King's Lynn, Norwich, and Sheffield in the three year period, 1982–4. Plasma samples were collected in cooled tubes, centrifuged at 4°C within

30 minutes and the separated plasma was stored at −20°C. Triiodothyronine was measured on 928 samples using a sensitive and specific radioimmunoassay (Gamma-B T3 Kit, RIA (UK)). Other thyroid hormones were not measured in this study.

Surviving infants were invited to a follow up examination at 18 months from expected date of delivery. All infants from the East Anglian centres (97% follow up rate on survivors) were examined by RM, who also organised the follow up in Sheffield. A medical and developmental history and full physical and neurological examinations were undertaken for each infant. Head circumference, naked weight, and supine length were measured and the Bayley mental and motor scales were administered to each infant[23]; the scores were calculated using the infant's age from expected date of delivery. The Bayley mental scale, however, like most tests of mental ability in young children, requires age appropriate manipulative skills and therefore children with cerebral palsy cannot be assessed satisfactorily. A further questionnaire based test was applied: the academic scale of Developmental Profile II,[24] which is based on items largely independent of fine manipulative skills at this age and permitted inclusion of infants with cerebral palsy. This test was used to derive an 'IQ equivalent'.

Statistical analyses included multiple regression, logistic regression, χ^2 test, Student's *t* test, and the Mann-Whitney rank sum test.

Results

In this cohort of 280 infants below 1850 g birth weight, plasma samples were analysed for triiodothyronine concentrations at 1–3 days, 4–7 days, and then at weekly intervals until discharge from hospital or until they attained 2000 g body weight. As not all infants contributed to the data at each time period and because they spent varying lengths of time in the study, data have been treated as cross sectional.

Plasma triiodothyronine concentrations were low in the first three days postnatally, median (lower quartile, upper quartile) 0·40 (0·23, 0·63) nmol/l. By the fourth week, median triiodothyronine concentrations had risen more than twofold to 0·86 (0·63, 1·17) nmol/l ($p<0·0001$) and, in those infants still remaining in hospital, they rose further to 1·20, (0·86, 1·45) nmol/l beyond eight weeks ($p<0·01$).

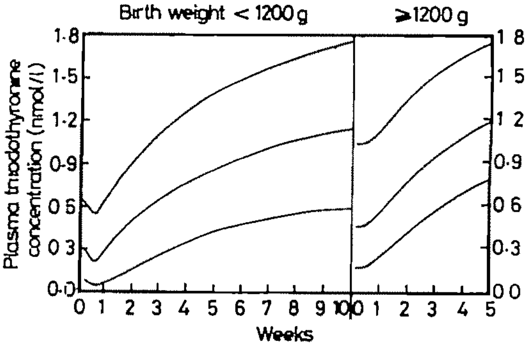

Fig 1 *Postnatal changes in plasma triiodothyronine concentrations in preterm infants above and below 1200 g, the smoothed curves presented are the 10th, 50th, and 90th centiles.*

Fig 1 shows that infants above and below 1200 g differed in plasma triiodothyronine concentration. In the first three days, the smaller infants had significantly lower median triiodothyronine values: 0·31 (0·15, 0·45) nmol/l compared with 0·48 (0·34, 0·68) nmol/l in the infants of larger birthweight ($p<0·005$). The rate of rise of plasma triiodothyronine postnatally was related to birth weight: in infants under 1200 g birth weight, plasma triiodothyronine concentration rose by a mean (SE) of 0·11 (0·01) nmol/week compared with a gain of 0·17 (0·01) nmol/week in those with birth weight ≥1200 g ($p<0·02$). Median plasma triiodothyronine concentrations tended to fall during the first week in infants below 1200 g (see fig 1). Though this fall did not reach significance, 77% of individual infants below 1200 g, and 50% of those above 1200 g, showed a fall in plasma triiodothyronine concentration rather than a rise during the first week. More detailed analysis, however, failed to show that this fall was more likely to occur in infants with severe lung disease, requiring mechanical ventilation for more than five days.

A reference lower limit of normal triiodothyronine concentration of 0·7 nmol/l for premature babies beyond 14 days[5] was achieved by the fourth week in 100% of healthy (non-ventilated) infants over 1500 g and in 81% of non-ventilated babies above 1200 g; but in sick ventilated babies below 1200 g only 34% had achieved this value.

A number of factors were analysed for their relationship with the lowest recorded values of plasma triiodothyronine in each of the 280 subjects. In a regression model with the number of days of ventilation, birth weight, gestation, sex, mode of delivery (vaginal compared with caesarean), Apgar score at 5 minutes, and maternal toxaemia as independent variables, it was found that duration of ventilation ($p<0·0001$), low birth weight ($p<0·001$), and vaginal delivery ($p<0·03$) were independently associated with lower plasma triiodothyronine concentration (dependent variable); see table 1. In addition, when plasma triiodothyronine was coded

Table 1 *Summary of factors examined for their relationship with low plasma triiodothyronine concentration (lowest recorded concentration under 0·3 nmol/l)*

*Factors independently associated with low plasma triiodothyronine**
Low birth weight
No of days of ventilation
Death, to 18 months†
Mental and motor developmental scores at 18 months (see table 2)
Vaginal delivery

Factors not associated with low plasma triiodothyronine
Weight, length, and head circumference gain in neonatal period
Weight, length, and head circumference at 18 months
Small for dates
Sex
Necrotising enterocolitis
Cerebral palsy

*After adjustment for key antenatal and neonatal factors
†Association not significant after adjustment for differences in requirement for mechanical ventilation between infants with high and low plasma triiodothyronine concentrations

as a dichotomous variable (see below), a plasma triiodothyronine concentration of under 0·3 nmol/l was less likely to occur in babies whose mothers had been given steroids before delivery (using logistic regression, p<0·02).

Mental development (measured by the Bayley mental scale) at 18 months was the principal outcome response of interest in this study. In a preliminary analysis, the lowest triiodothyronine concentration recorded for each subject was a better predictor of later development than the value at any particular postnatal age or the rate of rise of plasma triiodothyronine concentrations postnatally. Analysis of raw data showed a significant relationship between mental developmental index and the lowest triiodothyronine concentration recorded, but this relationship was non-linear as shown in fig 2 with the scores rising sharply when minimum triiodothyronine concentrations exceeded 0·3 nmol/l. The mean (SE) score in infants with triiodothyronine concentrations under 0·3 nmol/l was 92·3 (3·1) compared with a mean of 102·7 (1·5) in infants with minimum triiodothyronine concentrations above 0·3 nmol/l (p<0·01). For the analyses below, subjects were grouped according to whether their lowest triiodothyronine concentration was above or below 0·3 nmol/l.

The relationship between mental developmental index and the lowest concentration for triiodothyronine (above or below 0·3 nmol/l) was explored further by adjusting for sex, birth weight, gestation, small for dates status, mode of delivery, Apgar score at 5 minutes, number of days of ventilation, and maternal toxaemia. Even after these adjustments, infants whose plasma triiodothyronine fell below 0·3 nmol/l had a score that was 8·3 points lower than those whose recorded plasma triiodothyronine was consistently above this value (p=0·022; table 2). The only other independent variable in the model which related significantly to the mental developmental index (dependent variable) was days of ventilation (p<0·04). After adjusting for the factors

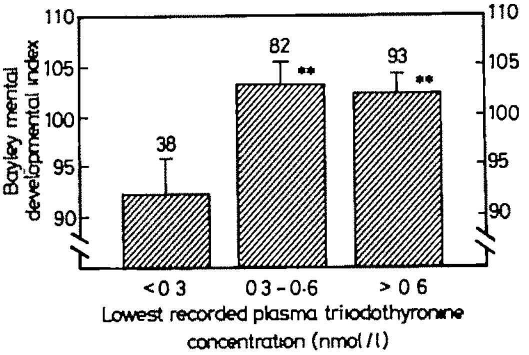

Fig 2 *Relationship between the lowest recorded value of plasma triiodothyronine concentration and Bayley mental developmental index at 18 months' corrected age. Triiodothyronine concentrations are divided into three categories: (i) <0·3 nmol/l, (ii) 0·3 to 0·6 nmol/l, and (iii) >0·6 nmol/l; scores for the mental development index are mean (SE) (No above each data bar). **=p<0·01 for difference between score in category (i) and either (ii) or (iii).*

Table 2 *Developmental disadvantage seen in surviving preterm infants whose lowest recorded plasma triiodothyronine concentration fell below 0·3 nmol/l (compared with those with lowest plasma triiodothyronine above this value), after adjusting for birth weight, gestation, days of ventilation, sex, Apgar score at 5 minutes, and mode of delivery*

Developmental test	*No of subjects*	*Developmental disadvantage (points) for infants with plasma triiodothyronine concentration <0·3 nmol/l (95% confidence interval)*	*p Value (from regression model)*
Bayley mental developmental index	213	8·3 (1·1 to 16 7)	0 022
Bayley psychomotor developmental index	210	7 4 (1 6 to 13·2)	0 012
Academic scale of developmental profile II (IQ equivalent)	226	8 6 (2·0 to 15 2)	0 010

listed above, a minimum triiodothyronine concentration of under 0·3 nmol/l also predicted Bayley motor development (7·4 point disadvantage: p=0·012) and IQ equivalent (8·6 point disadvantage; p=0·010); the latter test (see above) permitted inclusion of infants with cerebral palsy (13 cases).

Mortality rates (up to 18 months) were significantly related to plasma triiodothyronine concentration; in infants whose triiodothyronine fell below 0·3 nmol/l, 14 out of 61 (23%) died, compared with 12 out of 219 (6%) in those whose plasma triiodothyronine remained above this concentration (by χ^2 test, p< 0·0001). After adjusting for birth weight and gestation, the increase in mortality rate in the group with a lower plasma triiodothyronine concentration was diminished but still significant (p<0·02); and after adjusting further for requirement for mechanical ventilation, the relationship between plasma triiodothyronine concentration and mortality was lost.

No association was found between low plasma triiodothyronine concentrations and somatic growth; the outcome responses examined included head circumference, length and weight gain in the neonatal period, and head size, length, and body weight at 18 months' corrected age (table 1). In addition no relationship was observed between plasma triiodothyronine concentration and necrotising enterocolitis in the neonatal period or cerebral palsy at follow up (table 1).

Plasma total protein concentration was available for all the samples analysed for triiodothyronine. The relationship between triiodothyronine and later development was not influenced by adjusting for plasma protein at the time that the sample was taken.

Discussion

The principal finding in this follow up study on 280 preterm infants was the major association between low plasma triiodothyronine concentration and later development. Infants in the study were monitored weekly for plasma triiodothyronine concentrations during their hospital stay; those whose lowest recorded value was less than 0·3 nmol/l had significantly lower scores on the Bayley mental scale, Bayley motor scale, and on the academic scale of the questionnaire based test, Developmental Profile II, even after adjustment for a range of key maternal, perinatal, and neonatal factors.

The magnitude of the association between low plasma triiodothyronine concentrations and developmental scores was surprising. Examination of raw data showed a 10·4 point disadvantage in the Bayley mental developmental index for infants whose plasma triiodothyronine concentrations fell below 0·3 nmol/l (about 20% of the population studied). Even after statistical adjustment for birth weight, gestation, number of days of ventilation, and other important factors associated with impaired development, an 8·3 point disadvantage remained. Corresponding disadvantages were found (after adjustment) for motor development (7·4 points), and IQ equivalent (8·6 points). It was interesting that the latter test, which permitted inclusion of cases of cerebral palsy, gave remarkably similar results to those obtained from the Bayley mental scale, despite the fundamentally different nature of the two tests. Furthermore, in each of the three developmental tests, a low triiodothyronine concentration was the most significant factor analysed, greatly exceeding the predictive value of birth weight or gestation. Only the number of days of ventilation, in the Bayley mental developmental index, came close to a low plasma triiodothyronine concentration in this respect.

A number of investigators have raised the possibility that reduced plasma thyroid hormone concentration may play a major part in potentiating respiratory disease[9 10 12–14]; in this study, however, the developmental effects observed were independent of respiratory illness (as measured by days of ventilation required).

Our data contrast with those of other workers who have not found developmental consequences of low triiodothyronine concentrations.[19 21] Large sample sizes, however, are required to detect such developmental differences. From our own studies, we have calculated that the sample size required to detect an eight point difference in Bayley mental scale scores between two groups of babies (as detected here) is 150 subjects (<5% significance and 80% power). This could account for the absence of developmental effects seen at one year in the controlled double blind study of thyroid hormone replacement in premature babies conducted by Chowdhry *et al* on only 23 subjects.[21]

In this study we measured total triiodothyronine and not 'free' triiodothyronine. We have considered that our findings on neurodevelopment might relate to low thyroglobulin concentration, rather than to low thyroid hormone concentration in preterm infants. We did establish that total plasma protein concentration was not independently related to development, however, and that adjusting for plasma protein concentration did not influence the relationship between plasma triiodothyronine and developmental scores.

Somatic growth might be influenced by thyroid concentrations in several ways: for instance, by effects on energy metabolism, gut maturation, or respiratory illness (see below). We found no relationship, however, between plasma triiodothyronine concentration and head circumference, length, or weight gain in the short term; or head circumference, length, or body weight at 18 months' corrected age.

We considered that low thyroid hormone concentrations might cause an increased incidence of necrotising enterocolitis as a result of a reduced rate of gut maturation[15]; but no relationship between plasma triiodothyronine and necrotising enterocolitis was observed.

The death rate of infants with plasma triiodothyronine concentrations falling below 0·3 nmol/l was over four times higher than in those with persistently higher triiodothyronine concentrations. This association was reduced after adjusting for differences in birth weight and gestation between the groups with higher and lower plasma triiodothyronine concentrations, and was abolished after adjusting for the requirement for mechanical ventilation. This observation could be interpreted as an indirect effect of low plasma triiodothyronine concentration on mortality, through potentiation of respiratory disease, which is the major cause of death in preterm infants. This concept is supported by a body of experimental data on the effects of thyroid hormones on surfactant synthesis and lung maturation.[12–14] Indeed, in this study, after adjustment for other factors, there was a strong correlation between low triiodothyronine and duration of respiratory assistance, though whether or not low triiodothyronine concentration is a cause or effect of lung disease in preterm infants is still unresolved.

Whether aspects of the routine management of preterm infants influence plasma triiodothyronine concentrations, is currently under investigation. Our preliminary (unpublished) studies suggest that the incidence of very low plasma triiodothyronine concentrations, that are seen in some babies, may be independently related to low nutrient intakes. Conversely, maternal treatment with steroids appeared to have a prophylactic effect on the occurrence of plasma triiodothyronine concentrations under 0·3 nmol/l.

Our data confirm, on a large cohort, that preterm infants frequently have low plasma triiodothyronine concentrations in the postnatal period; and the pattern of postnatal changes has been defined for reference purposes. Previous reference values for triiodothyronine have often been based on relatively large, well, premature babies, and from one such study a value of 0·7 nmol/l could be taken as a lower limit of the range.[5] By the fourth week 100% of well, non-ventilated preterm infants over 1500 g birthweight in this study had exceeded that value; but of the infants below 1200 g, only 41% had exceeded it (34% in those who were ventilated), and 24% had still not attained this value by the eighth week.

There is still considerable debate on whether preterm infants, especially those who are sick or of very low birth weight, should receive routine treatment with thyroid hormones. In favour of this approach are the known, major adverse consequences of thyroid hormone deficiency in other circumstances. Against it are the arguments that 'hypothyroxinaemia of prematurity' may not have the same pathophysiological importance as in older subjects, and that a pharmacologically induced increase in metabolic rate might dissipate critical energy reserves and raise the requirement for oxygen Furthermore, thyroid hormones are potent biological triggers, which could have unpredictable effects if given unnecessarily. The disappointing results from some outcome studies may have added further weight to these counter arguments.[19 21] While low plasma triiodothyronine concentration is strongly predictive of developmental outcome in this study, the relationship may not be causal. Nevertheless, the strength and magnitude of the association clearly warrant further investigation, and we suggest that larger intervention studies, targeted to detect realistic differences in later development, are now indicated. The children in this study are part of a larger cohort being followed up indefinitely, and we shall be able to assess the longer term significance of the poor developmental scores seen at 18 months in association with low neonatal plasma triiodothyronine concentrations

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Increased recall rate at screening for congenital hypothyroidism in breast fed infants born to iodine overloaded mothers

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SUMMARY Skin disinfection with povidine-iodine (PVP-I) is widely used in obstetrics. We evaluated the influence of PVP-I in mothers at delivery on the serum thyroid stimulating hormone concentrations of their infants at the time of screening for congenital hypothyroidism. The study covered 4745 infants who were either breast fed (3659, 77%) or bottle fed (1086, 23%); 3086 (65%) of them were born to mothers with no iodine overload (controls) and 1659 (35%) to mothers with iodine overload. Compared with the control group, the breast and bottle fed infants born to mothers with iodide overload had a shift of neonatal thyroid stimulating hormone concentration towards high values. The shift was maximal in the breast fed infants with a 25 to 30 fold increase in the recall rate at screening for congenital hypothyroidism (serum thyroid stimulating hormone >50 mU/l) while in the bottle fed infants, the recall rate was barely modified. In conclusion, the use of PVP-I in mothers at delivery induces a transient impairment of thyroid function in their infants, especially if breast fed. This situation is detrimental to screening for congenital hypothyroidism. Consequently PVP-I is not recommended in obstetrics.

Skin disinfection with povidone-iodine (PVP-I) is widely used in obstetrics in epidural anaesthesia or caesarean section. This procedure results in iodide overload of the mother due to cutaneous absorption of iodine.[1] Iodide readily crosses the placenta[2] and is actively concentrated in the mammary gland.[3] Consequently, newborn infants born to mothers treated with PVP-I are also exposed to iodine overload, especially if breast fed.[4]

The thyroid gland of newborns is highly sensitive to the blocking effect of excess iodide on thyroid hormone synthesis, and a raised concentration of serum thyroid stimulating hormone is the most reliable index of impairment of thyroid function.[5] The objective of the present work was to evaluate the influence of cutaneous application of PVP-I in mothers at delivery on the concentrations of thyroid stimulating hormone in their infants at the time of screening for congenital hypothyroidism. In order to appreciate the specific role of the iodine contained in breast milk, a comparative study was performed between breast and bottle fed infants.

Patients and methods

The study included 4745 (96%) of the 4923 infants born in our maternity ward during a two year period. Of the 178 infants who were not included in the study, three were omitted because they had permanent congenital hypothyroidism due to thyroid agenesis with an appreciably raised serum thyroid stimulating hormone concentration and a low thyroxine concentration at screening and diagnosis. One hundred and seventy five (45 full term and 130 premature infants) were omitted because they were neither breast nor bottle fed: they were severely ill and received total parenteral nutrition until at least the fifth day of life. None of these 175 infants had a serum thyroid stimulating hormone concentration >50 mU/l at the time of screening for congenital hypothyroidism.

The 4745 infants under study were investigated on the fifth day of life at the time of screening for congenital hypothyroidism. As shown in table 1 they were distributed in several groups on the basis of the

Table 1 *Definition of the groups of newborn infants under investigation*

	Breast fed	*Bottle fed*	*Total (%)*
No iodine overload	2358	728	3086 (65)
Epidural anaesthesia	980	283	1263 (27)
Caesarean section	321	75	396 (8)
Total (%)	3659 (77)	1086 (23)	4745 (100)

type of feeding and the absence or presence of iodine overload: 3659 (77%) of the infants were breast fed and 1086 (23%) were bottle fed, 3086 (65%) were born to mothers with no iodine overload, 1659 (35%) were born to mothers with iodine overload due to the cutaneous application of PVP-I at delivery for epidural anaesthesia or caesarean section. In the former, a cutaneous surface of about 900 cm^2 was covered by one single application of PVP-I. In the latter, the whole abdominal wall was covered by three applications of PVP-I. The 10% solution of PVP-I used contained 10 mg of iodine/ml.

All the newborn infants were submitted to systematic neonatal screening for congenital hypothyroidism; serum thyroid stimulating hormone concentration was used as the primary screening test. When thyroid stimulating hormone concentration was above 20 mU/l serum thyroxine was measured in a second step from the initial blood spot. The criteria used for recalling an infant under suspicion of congenital hypothyroidism were a serum thyroid stimulating hormone concentration of >50 mU/l or a thyroid stimulating hormone concentration between 20 and 50 mU/l associated with a serum thyroxine concentration of <64 nmol/l.[6] Further investigation included clinical, biological, and radiological assessments, and when necessary the infants were scanned. Serum thyroid stimulating hormone and thyroxine were measured in duplicate by specific radioimmunoassay: at screening on blood spots dried on filter paper (the sensitivity was 40 mU/l for thyroid stimulating hormone and 13 nmol/l for thyroxine) and at recall on serum (the sensitivity was 0·4 mU/l for thyroid stimulating hormone and 13 nmol/l for thyroxine).[7]

Statistical analyses determined the frequency distribution of serum thyroid stimulating hormone concentrations in the whole infant population under study and compared this distribution in the different groups. The frequency distributions were compared by χ^2 tests.

Results

The frequency distribution of serum thyroid stimulating hormone concentration in the 4745 infants studied is shown in fig 1. The distribution was asymmetrical and skewed towards low values: 4311 (91%) of the values were <10 mU/l, 388 (8%) were moderately raised between 10 and 50 mU/l, and as many as 46 (1%) of the infants had a serum thyroid stimulating hormone >50 mU/l and were thus recalled. None was recalled on a basis of a thyroid stimulating hormone concentration between 20 and 50 mU/l associated with a thyroxine concentration <64 nmol/l.

The frequency distributions of serum thyroid stimulating hormone concentrations in the different groups of infants considered are shown in fig 2: in the breast fed infants born to mothers treated with PVP-I, there was a clear cut shift of serum thyroid stimulating hormone towards high values.

The recall rate increased from 0·1% in the absence of iodine overload to 3·2% in case of epidural anaesthesia and 2·7% in case of caesarean section. Serum thyroxine concentration at screening and at the time of recall for control examinations was normal in all infants. In the bottle fed infants, there was also a slight shift towards raised thyroid

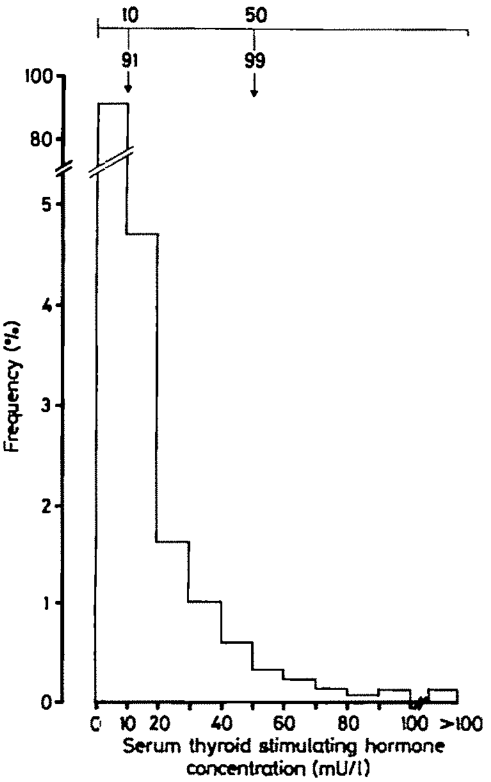

Fig 1 *Frequency distribution of the serum thyroid stimulating hormone concentration (mU/l) on day five in all newborn infants under investigation (n=4745).*

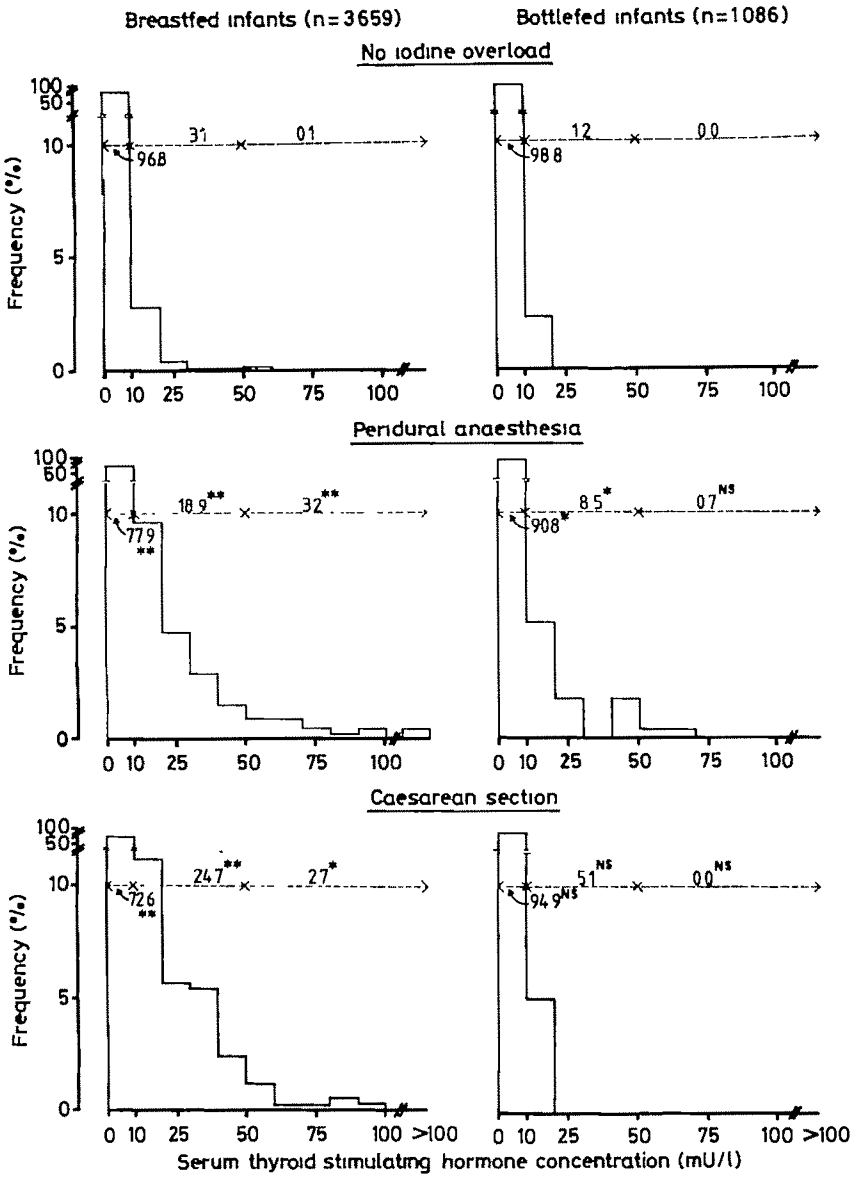

Fig 2 *Comparison of the frequency distributions of the serum thyroid stimulating hormone concentration (mU/l) on day five in the different groups of newborn infants considered. The numbers on the dotted lines represent the cumulated frequencies of the serum thyroid stimulating hormone concentrations included in the arrows. The levels of significance both in breast and bottle fed infants refer to the comparison with the group with no iodine overload;* $*=p<0{\cdot}05$, $**=p<0{\cdot}01$

stimulating hormone concentrations in the iodine contaminated groups. The shift was much less pronounced, however, than in breast fed infants and the recall rate was barely modified.

Discussion

The present work shows that one cutaneous application of PVP-I in mothers at the time of delivery results in a shift of neonatal thyroid stimulating hormone towards raised concentrations both in breast fed and bottle fed infants. The shift is much more important in the case of breast feeding, where there is a 25 to 30 fold increase in the recall rate.

The cause of the shift in breast fed infants is obviously iodine overload. We have previously reported that there was a two and 12 fold increase in the iodine content of breast milk after the use of PVP-I for epidural anaesthesia and caesarean section respectively (table 2).[4] The shift in bottle fed infants probably results from moderate fetal iodine overload occurring between skin disinfection with PVP-I and delivery because of a transfer of iodine across the placenta

Chabrolle and Rossier have shown that the application of PVP-I directly on the skin of infants occasionally increases their serum thyroid stimulating hormone concentrations.[8] Our results indicate that the same phenomenon occurs when PVP-I is used in the mother before delivery.

In our study, all infants with moderately or appreciably raised serum thyroid stimulating hormone concentrations at screening had normal thyroxine at screening and all further investigations were also normal. Consequently, the raised serum thyroid stimulating hormone indicates a very transient state of compensated or subclinical hypothyroidism which, most probably will not affect the long term development of the infants [5 9] Our study, however, underlines the public health importance of these transient alterations In the newborn population under study, the recall rate was 1% instead of 0·2% in our screening programme.[10] In addition, there was a clear cut increase in the frequency of moderately raised thyroid stimulating hormone between 10 and 50 mU/l, which also indicates some impairment of thyroid function, although the infants were not recalled.

This high recall rate is detrimental to the screening programme and increases its cost because of the further investigations needed. It also appreciably increases the frequency of so called 'false positives' at screening this is an unfavourable situation for a screening programme.[11] Finally, but of major importance, the high recall rate causes unnecessary psychological stress in many families. Long term effects of this recall on the mother-infant relationship have been well documented; these adverse effects were present even when the results of the control examinations were normal.[12]

In conclusion, the use of PVP-I in mothers at delivery can result in a mild Wolff-Chaikoff effect in the infant, especially if breast fed. Impairment of thyroid function is transient and probably without major consequences. It unnecessarily increases the recall rate, however, and consequently the cost of the screening and stress on families. Therefore PVP-I is not recommended in obstetrics.

Table 2 *Iodine content of maternal milk at the fifth postnatal day with and without iodine overload. (Modified from Chanoine et al[4])*

	Mean (SD) iodine concentration (μmol/l)
No iodine overload	0·75 (0·05)
Iodine overload after.	
Epidural anaesthesia	1·25 (0·1[illegible])
Caesarean section	9·93 (3·3[illegible])

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See letter from Chanoine *et al* in Correspondence column p 1297

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Methionyl human growth hormone in Turner's syndrome

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SUMMARY Sixteen girls with Turner's syndrome aged 7·9–15·2 years (bone ages 7·0–11·8 years) were given methionyl growth hormone (somatrem) 4 IU/m^2 body surface daily, corresponding to 0·9 IU/kg/week. During one year of treatment their mean (SD) height velocity increased from 3·4 (0·9) to 7·2 (1·7) cm/year and height prediction from 148·2 (4·4) to 150·0 (4·4) cm. All the girls except one had a height velocity increment of more than 2 cm/year and these velocities are above the age references for girls with Turner's syndrome. The girl with a low growth response had antibodies against growth hormone with high binding capacity (3·7 U/l). The height velocity increment was inversely correlated with age and bone age, but this might be partly due to the somewhat higher dosage/m^2 body surface and kg body weight that the younger patients were given because of the rounding off of the dose. The better results of our study compared with those of other workers who used similar dosages but did not give the drug as often suggest that giving it daily might have increased the growth response as it does in children deficient in growth hormone.

Turner's syndrome comprises a number of physical abnormalities including sexual infantilism, webbed neck, cubitus valgus, and poor growth velocity that results in short stature. The growth pattern has been well documented, and the reported mean adult height varies between 141·0 and 147·8 cm.[1–3]

The mechanism underlying this failure to grow is not known, but it is generally believed that the defect is primarily cellular.[4] Peak plasma concentrations of growth hormone have been reported as normal by some authors but as low by others after various pharmacological provocation tests.[5 6] Ross *et al*[7] studied the 24 hour growth hormone profiles in 30 patients with Turner's syndrome, and observed that between 9 and 20 years of age these girls had 24 hour growth hormone profiles with low integrated growth hormone concentrations, peak amplitudes, and peak frequencies compared with those of age matched controls. In contrast, these values were not significantly different between 2 and 8 years of age.

In a number of short term studies, treatment of patients with Turner's syndrome by human pituitary growth hormone (sometimes given simultaneously with anabolic steroids) gave divergent results concerning growth velocity.[8–14] Until recently wider use was impossible because the supply was limited, but since 1985 biosynthetic growth hormone produced by recombinant deoxyribonucleic acid (DNA) technology has been widely available. Biosynthetic methionyl human growth hormone (somatrem) in a supraphysiological dose given three times a week has been used for patients with Turner's syndrome with favourable results.[15 16] Similar results have been obtained with pituitary derived growth hormone.[17] So far there are no data on the effect of giving growth hormone daily, though in children with growth hormone deficiency this has been shown to improve the growth response.[18–20]

In this report we describe the response to somatrem 4 IU/m^2 body surface given subcutaneously once a day for 12 months.

Patients and methods

Sixteen girls with Turner's syndrome were entered into the study. For inclusion the children had to meet the following criteria age over 6 years, height more than 2·5 standard deviations below the mean for age,[21] a growth velocity below the 25th percentile for bone age,[22] and bone age less than 12 years assessed by the method of Tanner and Whitehouse (TW 2, 20-bones).[23] Patients were excluded if they had any endocrine or metabolic disorder, if they were taking other drugs, or if there was a suspicion of psychosocial dwarfism. The diagnosis of Turner's syndrome was confirmed by lymphocyte chromosoma analysis. Children with monosomy XO as well as with mosaicisms were included, unless the mosaicisms contained a Y chromosome. Ages ranged from 7·9 to 15·2 years (mean 11·7) and bone ages from 7·0 to 11·8 (mean 10·2) (table 1).

Two standard growth hormone provocation tests (the arginine infusion test and the exercise test), and a growth hormone releasing factor test were performed. Arginine hydrochloride (0·5 g/kg body weight to a maximum of 30 g) was given intravenously over 30 minutes. Blood was taken 30 minutes before the infusion, at the time it started, and then 15, 30, 45, 60, 90, 120, and 150 minutes later for determination of growth hormone concentrations. The exercise test comprised 30 minutes of strenuous physical exercise on a bicycle ergometer, and blood samples were taken from an indwelling venous catheter at the time the test started, and 10, 20, and 30 minutes later. For the growth hormone releasing factor test synthetic growth hormone releasing factor 1 µg/kg body weight was used (KabiVitrum, Stockholm, Sweden). Blood samples were taken 30 minutes before it was given, at the time it was given, and at 15, 30, 45, 60, and 120 minutes later. Determinations of growth hormone concentrations were performed in the laboratories of the participating centres. The various assays were compared through a series of test samples, and the growth hormone concentrations obtained from patients' serum samples were corrected for systematic assay differences.

The children received somatrem 4 IU/m^2 body surface daily; if the measurement was between 0·60 and 0·86 m^2, 3 IU were given, and if it was between 0·87 and 1·20 m^2, 4 IU were given. The mean (SD) growth hormone dose/m^2/week was 26·2 (2·4). Expressed as IU/kg/week this is equivalent to 0·92 (0·26) Somatrem was prepared by KabiVitrum AB (Stockholm, Sweden) in rubber sealed phials containing 4 IU (about 1·7 mg) as a sterile lyophilised powder containing 37 mg glycine and 0·7 mg sodium phosphate. The parents were carefully instructed about how to reconstitute the drug solution. Somatrem was injected subcutaneously by the children or the parents according to a standardised procedure, and the site of injection was changed daily. The children received no additional drugs except children aged over 13 who received low dose ethinyloestradiol (0·1 µg/kg body weight/day (cases 1, 8, 10, and 11).

Table 1 *Selected clinical data*

Case No	*Chromosomal pattern*	*Age (years)*	*Bone age*[23]	*Height*		*Weight*		*Taking ethinyl oestradiol*
				Cm	*Standard deviation score*	*Kg*	*% Of median weight for height*	
1	45 XO	14·1	11·7	134 1	−4·6	32·0	113 1	Yes
2	45 XO	12·5	11·8	123 5	−4 6	36 0	155 2	No
3	45 XO/46,X,r(X)	12·4	11 0	132·2	−3 3	36·7	134·4	No
4	46 XXq−*	10·5	8 5	115 5	−4·3	36 9	182 1	No
5	45 XO	9·3	9 7	122·2	−2 6	24·7	109 2	No
6	45 XO	7·9	7·0	110 1	−3 5	20·9	112·9	No
7	45 XO	12·9	11·2	130 3	−4·2	36 4	137·6	No
8	45 XO/46,X,r(X)	13·1	10·9	131·6	−4 2	34·7	128 5	Yes
9	45 XO	11·3	9·4	118·5	−4 5	20·1	94·3	No
10	45 XO	13·3	11·6	130 8	−4 9	32·2	120·5	Yes
11	46 X,i(Xq)	15·2	11·6	135 9	−5·1	34 1	116 3	Yes
12	45 XO/46,X,r(X)	11·4	9·4	119·5	−4 2	22·8	105·2	No
13	45 XO	10·1	9·8	120 6	−3 3	22 4	101 8	No
14	45 XO/46,XX	9·5	9·0	124 2	−2 5	28·4	120 8	No
15	45 XO	12·9	10·8	129 8	−4·3	32 8	125·2	No
16	45 XO	9·9	9·4	122 8	−2·9	26·7	116 4	No
Mean (SD)		11·7 (2·0)	10 2 (1 4)	125 1 (7 3)	−3 9 (0 81)	29·9 (6 1)	123 3 (21·6)	

*46,XXq−=46,XX,−X,+der(X) del(Q2[illegible] --- Q ter)

The response of height to somatrem was analysed by measuring height when standing with a Harpenden stadiometer after 4, 8, 12, 26, 39, and 52 weeks of treatment. The short term effect on growth velocity was investigated by measuring height after 4, 8 and 12 weeks of treatment. Heights were always measured at the same hour of the day, and the measurements were performed four times by each of two investigators. The average of the means of both investigators was used for further calculations. From six months onwards measurements were made by one investigator, and the mean of four measurements was used for further analysis.

Heights were expressed as standard deviation scores using the recent Dutch cross sectional references.[21] The growth velocity was expressed as cm/year and for comparison the velocity curves for girls with Turner's syndrome prepared by Ranke *et al*[24] were used. Sitting height was measured by standard techniques. The ratio sitting height:subischial leg length was transformed to a standard deviation score using the reference values from the Zurich longitudinal growth study (RH Largo and M Zachmann, personal communication). Weight was measured on an accurate scale and expressed as a percentage of the median for height.[21]

Skinfold thickness was measured at the left biceps, triceps, and subscapular site, according to standard procedures [25] The left arm circumference was measured halfway between the acromion and olecranon. The muscle/bone area (mm^2) in the left upper arm was estimated using the equation $\pi .(C/2\pi(b+t)/40)^2$, where C is the arm circumference (mm), b the biceps skinfold thickness (0·1 mm) and t the triceps skinfold thickness (0·1 mm). These values were compared with Dutch age references.[26] Radiographs of the hands were taken at 0, 6, and 12 months and assessed by one of the authors (AB) using the atlas of Greulich and Pyle[27] and the method of Tanner and Whitehouse.[23] Values for height were calculated using the tables of Bailey and Pinneau.[27]

Before the start of treatment, and at three monthly intervals during treatment, blood samples were taken for estimation of concentrations of haemoglobin, erythrocytes, leucocytes, platelets, and total eosinophils, leucocyte differentiation, and haematocrit. Biochemical assessment of serum samples included blood urea nitrogen and creatinine concentrations, alkaline phosphatase and transaminase activities, electrolytes, albumin, and thyroxine concentrations. Urine samples were analysed by routine methods for the presence of glucose, protein, blood, and sediment. Urinary concentrations of retinol binding protein were measured with the Hyland Disc nephelometer (Hyland, Nivelle, Belgium) by the technique of Renckens *et al.*[28] The antiserum used was rabbit antiretinol binding protein (Dako, Glostrup, Denmark) and the detection limit was 0·12 mg/l.

The immunological screening consisted of determinations of circulating immune complexes (CIq method[29]), antibodies against growth hormone and antibodies against *Escherichia coli* proteins. Most determinations of circulating immune complexes were done in the central laboratory of the blood

Table 2 *Growth velocity (cm/year)*

Case No	*Before treatment*	*During treatment*			*Increment after one year of treatment*
		0–3 Months	*0–6 Months*	*0–12 Months*	
1	2·6	6·8	5·9	6·2	3·6
2	3·4	4·8	5·8	4·1	0·7
3	2·5	6·1	6·8	6·1	3·6
4	5·0	7·0	7·0	7·2	2·2
5	4·3	7·4	8·8	8·1	3·8
6	3·4	10·3	10·0	10·1	6·7
7	3·1	8·0	6·2	5·9	2·8
8	3·7	9·7	6·0	5·7	2·0
9	3·2	7·6	7·0	6·3	3·0
10	2·9	6·2	4·6	5·7	2·8
11	1·6	10·8	6·9	6·2	4·6
12	3·1	9·2	7·6	8·4	5·3
13	3·3	10·0	8·2	7·9	4·6
14	3·2	11·5	9·1	10·1	6·9
15	3·6	8·4	8·2	7·1	3·5
16	5·3	13·2	11·0	9·7	4·4
Mean (SD)	3·4 (0·9)	8·6 (2·2)	7·4 (1·7)	7·2 (1·7)	3·8 (1·6)
Range	1·6–5·3	4·8–13·2	4·6–11·0	4·1–10·1	0·7–6·9

transfusion service in Amsterdam (normal range <7%) and some in the laboratories of the Free University in Amsterdam, and of the Erasmus University, Rotterdam (normal range <15%). Antibodies against growth hormone were measured at the endocrine laboratory of the Bergweg Hospital in Rotterdam by determining the percentage binding of ^{125}I labeled human growth hormone before and after the addition of 25 μU somatrem. In 75 controls the percentage binding ranged between 2 and 16·7%, and 0·5 and 11·5%, respectively. If the binding percentage was greater than 16·7% it was an indication that antibodies against growth hormone were present. If the binding was greater than 15% a Scatchard plot was made to determine the binding capacity and K value of the strongly binding and weakly binding antibodies. Antibodies against *E coli* proteins were measured by an enzyme linked immunosorbent assay (ELISA) by KabiVitrum (Stockholm, Sweden).

Results are expressed as mean (SD), except where indicated otherwise. The paired Student's *t* test and the Wilcoxon matched pairs signed rank test were used for the analysis of changes within the groups. The correlations between various measurements were made by Spearman's correlation test.

Results

Table 2 shows the individual growth velocities before and during treatment with somatrem, and the increments while receiving treatment. There was a significant increase in the mean growth velocity from 3·4 to 7·2 cm/year in the first 12 months ($p<0·001$). When compared with the Turner growth velocity reference curves[24] all growth velocities before treatment were within the reference range, whereas all growth velocities after the start of treatment except one were well above this range (fig 1). The mean cumulative growth velocities are shown in fig 2.

During the first year of treatment the mean (SD) increase in bone age was 1·0 (0·4) years when assessed by the method of Tanner and Whitehouse[23] and 1·1 (0·8) when assessed by that of Greulich and Pyle.[25] The increase in bone age assessed by the method of Tanner and Whitehouse was 0·4 (0·3) in the first semester, not statistically different from that in the second semester (0·6 (0·3)). According to the method of Greulich and Pyle the increase in bone age during the first semester was 0·2 (0·4), significantly less than that in the second semester (0·9 (0·6), $p<0·001$). The mean (SD) height prediction (based on the bone age readings with the Greulich and Pyle atlas and the Bailey Pinneau

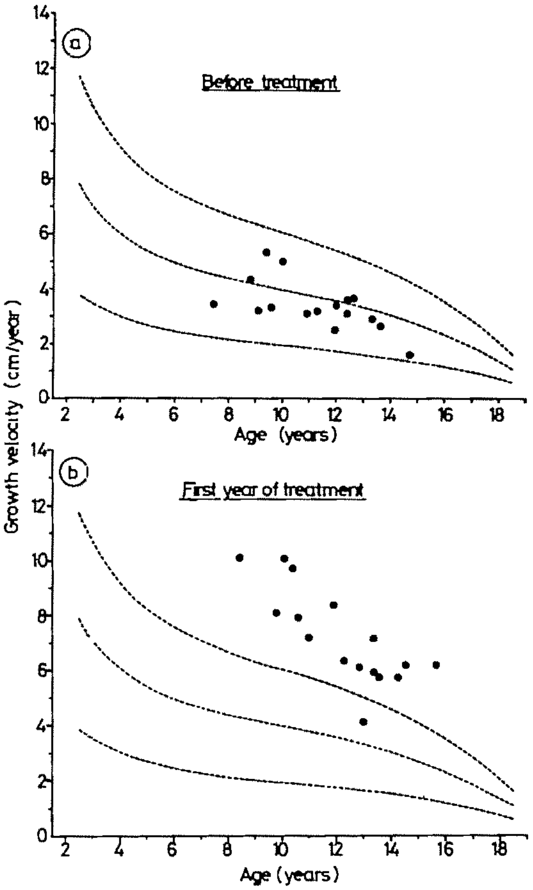

Fig 1 *Growth velocities before and during treatment compared with the growth velocity reference curves for Turner's syndrome.*[24]

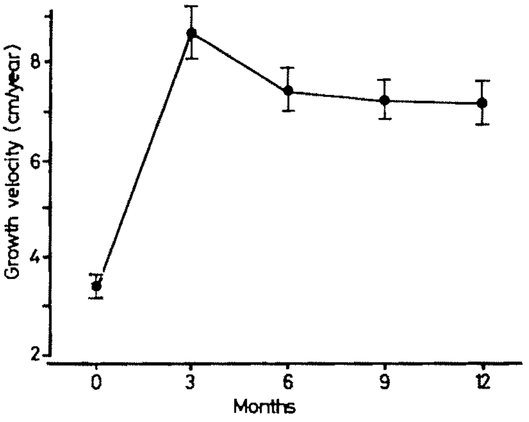

Fig 2 *Mean (SEM) cumulative growth velocities*

tables) increased from 148·2 (4·4) to 150·0 (4·4) cm (p=0·06).

There were no significant changes of the triceps, biceps, and subscapular skinfold thicknesses, weight for height, muscle/bone area, or the ratio of the sitting height:subischial leg length expressed as standard deviation score for bone age.

There was a weak but significant negative correlation between the growth velocity increment after 12 months of treatment and chronological age (r=−0·51, p<0·05), and bone age (r=−0·55, p<0·05). The rounding off of the growth hormone dose meant that the average older girls received less growth hormone per m^2 body surface or kilogram body weight than the younger girls. This is illustrated by the negative correlation between age and growth hormone dose in IU/kg/week (r=−0·67, p<0·01). As the height velocity increment is also correlated with the growth hormone dose in IU/kg/week (r=0·54), it is possible that the inverse correlation between height velocity increment and age is at least partly a dosage effect. Neither the growth velocity before treatment nor the delay in bone maturation correlated with the growth velocity increment after 12 months of treatment. The growth velocity increment after four weeks did not correlate significantly with the increment after 12 months (r=0·43), but did after 8 and 12 weeks (r=0·57, p<0·05, and r=0·73, p<0·01, respectively).

The maximum growth hormone concentrations after arginine infusion were between 2 and 68 mU/l (mean 24), after exercise between 1 and 50 mU/l (mean 22), and after growth hormone releasing factor between 7 and 137 mU/l (mean 40). In six girls (aged 9·3 to 13·8 years, mean 11·9) the peak growth hormone concentrations during the two provocation tests were below 20 mU/l. When the patient with the high concentration of antibodies against growth hormone was excluded, the mean (SD) increment was 3·0 (0·7) cm-year compared with 4·5 (1·5) cm/year in the remaining children.

To see if there were any predictors of the effect of treatment with growth hormone in patients with Turner's syndrome we calculated the correlation coefficients of the peaks of the different growth hormone provocation test against the increment of height velocity as well as the height velocity itself. None of these correlated significantly with the growth response

The haematological and biochemical measurements in blood and urine did not show any significant changes. The urinary excretion of retinol binding protein remained below the detection limit in all children. In seven of 15 patients antibodies against growth hormone were found during treatment. Binding capacity was low (<1·3 U/l) in six children. One child (case 2) showed antibodies against growth hormone with a high binding capacity of 3·7 U/l. She had a growth velocity increment of 0·7 cm/year, which is much lower than the mean growth velocity increment. In addition, her absolute growth velocity while receiving treatment (4·1 cm/year) was far below those of the other patients (fig 1). Her treatment was therefore changed to a non-methionyl growth hormone preparation after a year. Transient rises in concentrations of circulating immune complexes were noticed after three months of treatment in five girls (range 11–87%). Another girl had a high value after nine months of treatment (31%). After 12 months of treatment all measurements were within the normal range. In four of these six girls antibodies against growth hormone were found.

In eight children antibodies against *E coli* proteins were detectable before treatment, but the titres were low (0·1–0·8). During treatment the number of children in whom the antibodies were detected did not increase and the titres remained the same.

No adverse reactions were noted, compliance was good, and the girls were enthusiastic about the results. There were no problems with the daily injections of growth hormone.

Discussion

The effect of pituitary derived growth hormone on patients with Turner's syndrome has been described in a number of studies. Soyka *et al*[11] and Tanner *et al*[10] found little or no growth acceleration over a period of 12 months using doses as high as 18 mg (presumably 18 IU) and 20 IU per week. Stahnke *et al* reported that six of eight patients with Turner's syndrome did not benefit from treatment with growth hormone.[9] Other authors found significant increases in growth velocity in patients taking pituitary or biosynthetic growth hormone.[8 12–16] Rosenfeld *et al* also reported a good growth response in the second year of treatment.[30] In the period after treatment the growth velocity usually decreased to values before treatment, and in one study the acceleration during treatment was cancelled out by the deceleration after treatment.[10]

Ross *et al*[31] studied the dose response association between short term linear growth and growth hormone dosage, given three times a week. Lower leg length showed no increase with a growth hormone dose of 0·15 IU/kg/week, but increased significantly with doses of 0·45 and 1·35 IU/kg/week. The higher dose of 1·35 IU/kg was no more effective than that of 0·45 IU/kg. In our study, daily somatrem (0·9 IU/kg/week) resulted in a considerable increment in growth velocity, which is higher

Table 3 *Comparison of the results from different studies*

Study	*Mean dose of growth hormone (IU/kg/week*)*	*No of injections/ week*	*Mean (SD) age (years)*	*Growth velocity (cm/year)*	
				Before treatment	*Up to 12 months after treatment*
Rosenfeld *et al*[16]	Somatrem 0·9	3	3·1 (2·1)	4·5	6·6
Takano *et al*[15]	Somatrem 0·2–0·9	2–4	1[illegible]·5 (1·8)	3·6	5·5
Raiti *et al*[17]	Human pituitary derived growth hormone	3	Not known	3·2	5·9
Present study	Somatrem 0·9	7	1[illegible]·7 (2·1)	3·4	7·2

*Conversion factor 1 mg=2½ IU.

than the increments with 0·6–0·9 IU/kg/week given by three injections per week reported by other authors (table 3). When the results of Ross *et al* are extrapolated to one year periods, a dose of 0·9 IU/kg/week should have no better effects than a dose of 0·5 IU/kg/week. This suggests that the better results in our study are due to giving the doses more often. This is in line with the reports that in children deficient in growth hormone daily doses of growth hormone have more effect on growth than doses given three times a week.[8–10]

Takano *et al*[15] found antibodies against growth hormone in 60% of their patients at the end of 12 months of treatment with somatrem. In our patients the percentage was 73%. Only one child had antibodies against growth hormone with a high binding capacity, and this child also had a poor growth response.

Bone age advanced by 1·0 (0·4) years and the average height prediction increased by 1·8 cm. These preliminary results and the results of the American collaborative study[16 30] suggest that the increased growth velocity may result in higher final heights. Long term follow up is required however, to determine whether this will be the case.

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Plasma concentrations of gastrin and somatostatin after breast feeding in 4 day old infants

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SUMMARY The plasma concentrations of gastrin and somatostatin were measured by radioimmunoassay before and after breast feeding in healthy 4 day old infants who had been born at full term. The mean (SD) concentrations of gastrin and somatostatin before breast feeding were 120 (30) pmol/l and 35 (12) pmol/l, respectively. Breast feeding in these infants was not followed by increased concentrations of gastrin and somatostatin in peripheral blood. High preprandial peptide concentrations, as seen during the neonatal period may limit the further release of peptide after feeding.

The pattern of the release of gastrin induced by feeding changes during the neonatal period. The plasma gastrin concentration increases in response to the first feed of breast milk[1] or formula milk[2] in newborn infants aged 2–6 hours. No such increase, however, has been seen after subsequent feeds during the first week of life.[3] A possible explanation of why the gastrin concentration does not rise after feeding during this period could be the pressure of high concentrations of somatostatin, which is known to inhibit the release of gastrin. We therefore measured the plasma concentrations of gastrin and somatostatin before and after breast feeding in healthy 4 day old infants who had been born at full term.

Patients and methods

Thirty eight healthy infants (23 boys and 15 girls) were studied with the approval of the local ethical committee and the consent of the parents. All the babies had been born at full term after uncomplicated pregnancies. Their mean (SD) gestational age was 39 (1) weeks and birth weight 3468 (397) g. All infants were exclusively breast fed. Blood samples for determination of gastrin and somatostatin concentrations were collected at a mean (SD) of 4 (1) days of age. Thirty two infants were breast fed between 9 and 12 am and six between noon and 3 pm. This feed took place 3 (1) hours after the preceding feed and according to the mother was demanded by the infant. The infants were allowed to suck to satiety. The mean (SD) duration of feed was 25 (10) minutes and the amount of milk ingested, calculated by weighing 19 infants, was 55 (30) ml.

Samples of 1·5 ml of venous blood were drawn from the backs of the hands with open needles as part of routine metabolic screening. The samples were collected in one group of infants (n=12) before and 10 minutes after feeding, in a second group (n=14) before and 30 minutes after feeding, and in a third group (n=12) before and 60 minutes after feeding. Bloods samples were collected in ice cold plastic tubes containing 10 IU heparin and 500 KIE aprotinin/ml blood and centrifuged at 4°C within 30 minutes of collection. The plasma samples were stored at −20°C until analysed for concentrations of gastrin and somatostatin.

Gastrin concentrations were determined by radioimmunoassay using antiserum 2604.[4] as described by Nilsson. These antibodies recognise gastrin-17 and gastrin-34 as well as sulphated and unsulphated forms of gastrin with the same potency. Somatostatin concentrations were measured by the assay described by Efendic *et al*[5] after separation from large plasma proteins with SEP-PAK C18 cartridges (Water Associates Inc).

Data are given as mean (SD). Statistical analyses were by Student's *t* test. Correlations between variables were analysed by simple regression analysis.

Results

Preprandial plasma gastrin (n=34) and somatostatin (n=38) concentrations were 120 (30) pmol/l and 35 (12) pmol/l, respectively. These were not related to postnatal age nor to the time intervals since the preceding meal. No significant rises occurred postprandially in gastrin or somatostatin concentrations (figs 1 and 2). There was no association between gastrin and somatostatin concentrations either before or after breast feeding.

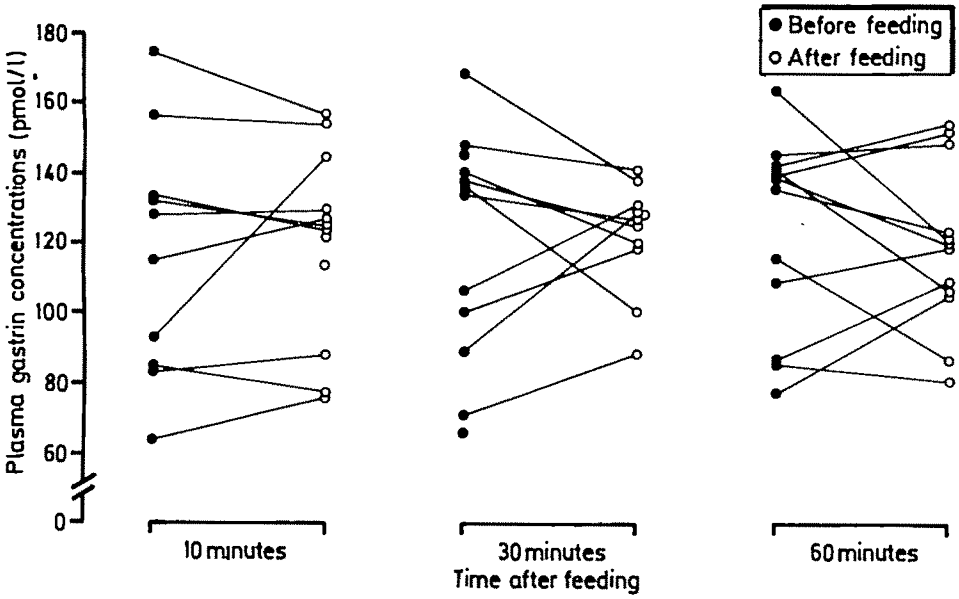

Fig 1 *Individual plasma gastrin concentrations in three groups of infants before and after breast feeding.*

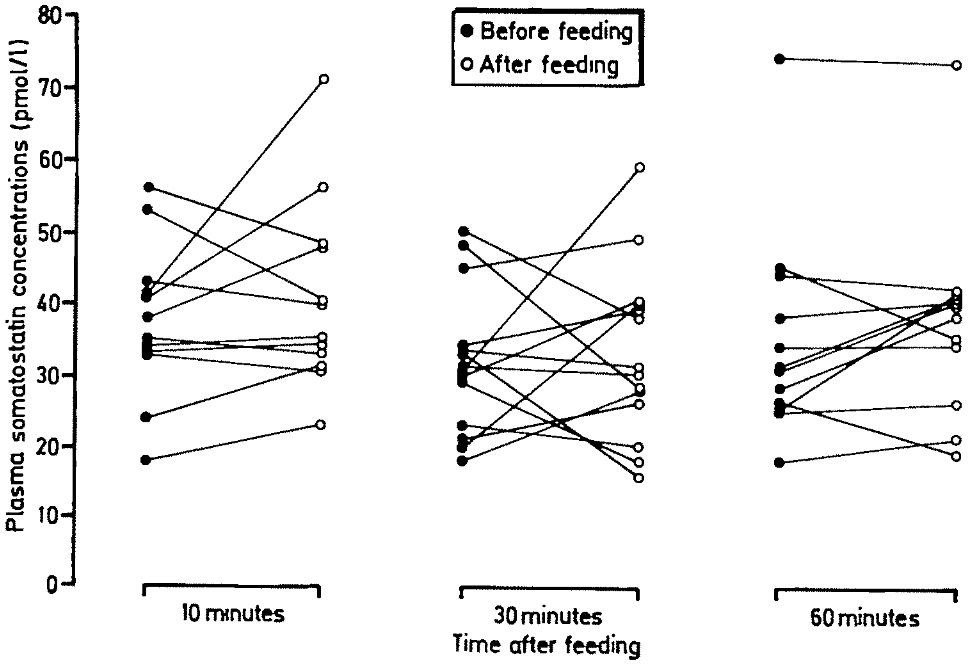

Fig 2 *Individual plasma somatostatin concentrations in three groups of infants before and after breast feeding*

Discussion

We found no increase in gastrin concentrations after breast feeding in 4 day old infants. This is in accordance with previous studies performed at a similar postnatal age that reported no change in the concentration of gastrin after breast feeding or bottle feeding in infants born at full term,[6] or after tube feeding in infants born prematurely.[3]

The absence of an increase in gastrin induced by feeding in infants has been ascribed to the high basal concentration of gastrin that is present during the neonatal period.[3] The first feed given to newborn infants is followed by a postprandial increase in plasma gastrin concentration,[1 2] though no such response is seen on the second or the sixth days, by which times basal plasma gastrin concentrations have increased 10 fold compared with the concentrations before the first feed.[5 7] The comparative hypergastrinaemia could also partly explain why infants do not respond by secreting acid after being given pentagastrin or histamine during the neonatal period[8 9] or why non-nutritive sucking (a stimulus that has been suggested as triggering the release of other vagally controlled peptides such as insulin), failed to influence plasma gastrin concentrations in newborn infants.[10]

Because gastrin exerts trophic effects on the gastric mucosa,[11] the rapid growth of the stomach that occurs in mammals during the first week of life[12] could be associated with the high gastrin concentrations during the neonatal period.

Circulating somatostatin is principally derived from the stomach[13] and gastric somatostatin is produced partly in antral cells that are in open contact with the gastric lumen that are sensitive to intragastric pH.[14] Somatostatin from these cells exerts an inhibitory effect on the release of gastrin by local paracrine mechanisms. Most gastric somatostatin cells are found in the corporeal mucosa and here the peptide is associated with the regulation of the secretion of gastric acid from the parietal cells. Gastric somatostatin is released in response to nutrients in the stomach and is influenced by vagal nerve activity and antral pH.[13]

In the present study basal concentrations of somatostatin were in the same range as those described in premature babies and they were therefore high when compared with preprandial concentrations in adults.[15] We did not find any significant change in somatostatin concentrations before or after breast feeding. This is in contrast to the results of Sann *et al*, who found that tube feeding in 2 day old premature infants induced a decrease in postprandial somatostatin concentrations.[15] A comparison between their results and ours, however, is difficult because gestational age, postnatal age, and mode of feeding were different in the two studies

The high plasma concentrations of somatostatin are likely to reflect enhanced secretion of somatostatin by the gastric mucosa. Because somatostatin inhibits the release of gastrin, an increase in the release of antral somatostatin may contribute to the unresponsiveness of the gastrin cells during the first week of life. Furthermore, as somatostatin inhibits secretion of acid from the parietal cells, a high rate of secretion of somatostatin in the corporeal mucosa might explain (in addition to the increased plasma gastrin concentrations) why pentagastrin and histamine fail to induce secretion of acid during the neonatal period [9 10] In newborn and tube fed preterm infants a substantial release of somatostatin into the gastric lumen occurs when the intragastric pH is low.[16 17] This somatostatin is probably derived from the antral somatostatin cells.[13] Because the present data show that circulating somatostatin concentrations are not increased after breast feeding, either there are no changes caused by feeding in the rate of secretion of antral somatostatin or, if there are, the responses are not reflected in changes in the circulating somatostatin concentrations of 4 day old infants.

In conclusion, this study shows that breast feeding in 4 day old infants is not followed by increased gastrin or somatostatin concentrations in peripheral blood. We suggest that the high plasma concentrations of the two peptides before feeding reflect a high degree of stimulation of the gastrin and somatostatin producing cells (even under basal conditions) during a period of life when intake of nutrients is high, and the rate of growth increases rapidly

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Immune complexes and Pseudomonas aeruginosa antibodies in cystic fibrosis

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SUMMARY Serum samples from 57 patients with cystic fibrosis were tested for the presence of IgG, IgA, IgM, IgE, and circulating immune complexes containing IgG, IgA, and IgM. Titres of class specific antibodies to *Pseudomonas aeruginosa,* and class specific antibodies to *Ps aeruginosa* in circulating immune complexes, were also measured. According to the Shwachman score the patients were divided into three clinical groups: group 1 – moderate and severe disease, group 2 – mild disease and group 3 – well. The results of the immunological investigations were correlated with the clinical state of the patients as assessed by the Shwachman score. Serum concentrations of IgG, IgA, and IgM were inversely correlated with the Shwachman score, but the differences between the groups were only significant for IgG and IgA. The same correlations were found for circulating immune complexes containing IgG and IgA. Antibodies to *Ps aeruginosa* could be detected in most of the patients' serum samples. IgA antibody specific to *Ps aeruginosa* was the most often raised, even in patients in group 3. It is therefore suggested that IgA antibody specific to *Ps aeruginosa* could be an early marker of colonisation by *Ps aeruginosa* and a sensitive measurement of infection with *Ps aeruginosa* in young children with cystic fibrosis. Moreover, in the circulating immune complexes, class specific antibodies to *Ps aeruginosa* were found in nearly half the patients. The highest titres of IgG and IgA antibodies specific to *Ps aeruginosa* in the circulating immune complexes were detected in the patients with the worst clinical state (group 1).

Chronic bronchial infection with *Pseudomonas aeruginosa* is a major complication of cystic fibrosis leading to respiratory failure and ultimately death. Though lung injury can be directly caused by bacterial invasion, the role of the host defence system in permitting infection is still not clear. Circulating immune complexes have been found in serum,[1] respiratory secretions,[2] and various tissues[3] of patients with cystic fibrosis, and there is some evidence that tissue damage by circulating immune complexes could be a critical factor in the pathogenesis and progression of the disease. These complexes include antigens and antibodies to *Ps aeruginosa* as well as to other respiratory pathogens.[4–6]

In this study we looked for disorders of humoral immunity that correlated with clinical state and the results of lung function tests. We therefore measured IgG, IgA, IgM, IgE, and circulating immune complexes containing IgG, IgA, and IgM in a group of patients with cystic fibrosis. We also measured titres of class specific antibodies to *Ps aeruginosa,* and class specific antibodies to *Ps aeruginosa* in circulating immune complexes.

Patients and methods

Serum samples were obtained from 57 patients attending a cystic fibrosis clinic (Zeepreventorium, De Haan, Belgium). The 31 boys and 21 girls were aged from 4 to 26 years (mean 14·1). In all patients the diagnosis of cystic fibrosis was confirmed by a positive sweat test. They all had pulmonary and pancreatic disease. Overall clinical state was assessed by the Shwachman score.[7] A maximum of 25 points was given for each of the following: chest radiograph, nutritional state, general activity, and physical examination. The lower the score, the worse the condition of the patient. Complete clinical evaluation at the time of the study was obtained.

According to the Shwachman score the patients were divided into three groups: group 1 comprised 14 patients with a mean age of 18·1 years and scores of less than 55 (moderate or severe disease); group 2 comprised 18 patients with a mean age of 13·9 years and scores of 55–70 (mild disease); and group 3 comprised 25 patients with a mean age of 11·8 years and scores of 70 or more who were well at the time of examination. At the time of the study *Ps aeruginosa* was cultured from the sputum of 49 patients. *Streptococcus pneumoniae* and *Staphylococcus aureus* were each cultured from one patient; these two patients were in group 3. In six patients in group 3 no bacterial growth was detected.

Lung function tests including forced expiratory volume in one second (FEV_1), total gas volume, and residual volume, were performed by whole body plethysmography.

Serum samples were also obtained from 14 healthy subjects who acted as controls; the samples were stored at −20°C until used.

Serum concentrations of IgG, IgA, and IgM were measured by laser nephelometry (Behringwerk). Serum concentrations of IgE were measured by a sandwich enzyme linked immunosorbent assay (ELISA) using a monoclonal antihuman IgE (Diagnostics Pasteur); this showed an excellent correlation (r=0·97) with the PRIST technique (Pharmacia). For normal values of IgG, IgA, IgM, and IgE, respectively, according to age, we used the standards of Stiehm and Fudenburg[8] and Kjellman.[9]

Circulating immune complexes were precipitated out of serum with polyethylene glycol 6000 (Merck) as previously described.[10] Briefly, serum samples were diluted 1/2 with phosphate buffered saline, and were precipitated and washed with 2·5% or 1·5% (IgM) polyethylene glycol. These precipitates were then dissolved in 0·1 M Tris buffered saline containing 1% bovine serum albumin (Sigma) and 0·1% Tween 20 (Merck).

The IgG, IgA, and IgM content of the circulating immune complexes were measured by quantitative ELISA of the polyethylene glycol precipitate as follows: polystyrene microtitre plates (Costar) were coated with 10 µg/ml of class specific antihuman immunoglobulin diluted in carbonate buffer (0·1 M, pH 9·6). Goat antihuman IgG and IgA (Tago), and rabbit antihuman IgM (Dako), were incubated overnight at 4°C, free binding sites were blocked with 150 µl of a 1% bovine serum albumin in carbonate buffer, incubated for 1½ hours at 37°C, and washed five times in physiological saline containing 0·1% Tween 20 in an automated microplate washer (Titertek, Flow Laboratories). One hundred microlitres of polyethylene glycol precipitate diluted with 0·1% Tween 20 was then added to the wells in duplicate. The immunoglobulin assays were calibrated with a standard protein preparation (Behring) diluted with 0·1% Tween 20. The microtitre plates were then incubated for 2½ hours at 37°C and again washed with physiological saline containing 0·1% Tween 20; the bound immunoglobulins were detected with 100 µl of horseradish peroxidase conjugates. For IgG, IgA, and IgM containing circulating immune complexes, the $F(ab')_2$ fragments of horseradish peroxidase antihuman IgG, IgA, or IgM, (Tago) were used. After incubation for two hours at 37°C the plates were washed again and the wells filled with 100 µl of 0·4 mg/ml orthophenylene diamine (Sigma) and 0·014% hydrogen peroxide in citrate phosphate buffer (0·1 M, pH 5·0). The colour reaction was stopped after five minutes with 50 µl 2 M sulphuric acid. Optical densities were measured with a microplate photometer (Titertek, Flow Laboratories) at 492 nm with a reference absorbance at 690 nm. The analysis of the calibration curve and the calculation of unknown factors were performed with a four parametric logistic model as previously described.[11]

Titres of IgG, IgA, and IgM antibodies to *Ps aeruginosa* in serum and circulating immune complexes were quantified with ELISAs. A reference strain of *Ps aeruginosa* from the American Type Culture Collection was submitted to three cycles of freeze thawing, then 20 minutes of sonication, before being diluted 1/100 in carbonate buffer and sonicated until no visible aggregates remained. A total of 100 µl of this antigen solution was coated overnight at 4°C on polystyrene microtitre plates. Free binding sites were then blocked with 150 µl of 1% bovine serum albumin in carbonate buffer and incubated at 37°C for 1½ hours. After five washings with physiological saline containing 0·1% Tween 20, 100 µl of serum, 2·5% polyethylene glycol, or 1·5% polyethylene glycol precipitates diluted with 0·1% Tween 20, were added. A pool of serum samples with strongly positive titres of IgG, IgA, and IgM antibodies to *Ps aeruginosa* was used as a standard. One hundred arbitrary units were attributed to the lowest dilution of standard used, 1/80 for IgA, and 1/40 for IgM antibodies, respectively. Ten units were attributed to the 1/2400 dilution of standard pool for IgG antibody to *Ps aeruginosa*. The remainder of the ELISA (colour development and analysis of the results) was performed as reported for the measurement of class specific circulating immune complexes.

In order to correct for non-specific precipitation of free antibodies to *Ps aeruginosa*, a reference group of 12 patients whose serum samples did not contain IgG, IgA, and IgM circulating immune complexes was constituted. These reference samples were used to determine 'cut off' concentrations (95th percentile) for antibodies to *Ps aeruginosa* in the polyethylene glycol precipitate.

IgE antibody to *Ps aeruginosa* was measured with a capture ELISA. Microtitre plates were coated with 100 µl of a 10 µg/ml solution of monoclonal antihuman IgE (Diagnostics Pasteur) in carbonate buffer. After incubation overnight at 4°C, 150 µl of 1% bovine serum albumin in carbonate buffer was added to each well and incubated for 1½ hours at 37°C. After five washings with physiological saline containing 0·1% Tween 20, 100 µl of serum samples diluted 1/5 with 0·1% Tween 20 were added to each well. Plates were then incubated for three hours at 37°C, washed, and 100 µl of antigens to *Ps aeruginosa* treated with avidin-biotin were added to each well. *Ps aeruginosa* lysate was treated with N-hydroxy-succinimide biotin (Sigma) by the method of Subba Rao *et al.*[12] After incubation for a further two hours at 37°C the microtitre plates were washed, and 100 µl of a 1/1000 diluted streptavidin peroxidase conjugate (Amersham) were added for 45 minutes at 37°C. Colour development was done as for the other ELISAs. These semiquantitative results were expressed as optical densities (arbitrary units) and calibrated with optical densities obtained from control serum samples.

Results of immunoglobulin, circulating immune complexes, and *Ps aeruginosa* specific antibody assays were transformed logarithmically because of the skewness of the data, and are shown as geometric mean (SD). Significance of correlations among the logarithmically transformed values were calculated by the Pearson correlation coefficient. For comparison between groups, non-parametric one way analysis of variance (Kruskal–Wallis) was used.

Results

Mean serum IgG, IgA, and IgM concentrations were inversely correlated with the Shwachman score (table 1). The differences among the groups were only significant for IgG and IgA. When compared with age matched control subjects most patients with raised concentrations of immunoglobulin were found to be in the group with the most severe clinical disease. Serum IgE concentrations differed significantly among the different groups, with the highest concentrations being in patients in group 2.

Concentrations of circulating immune complexes containing IgG and IgA were significantly increased compared with the control population (table 2), and were highest in the patients in group 1. Concentrations of IgM containing circulating immune complexes were not associated with clinical state, though they were raised in 16 (28%) of the patients. Concentrations of the different circulating immune complexes also correlated significantly with the different serum immunoglobulin concentrations (results not shown).

Antibodies to *Ps aeruginosa* of the IgG and IgA classes were found in most patients (table 3). There was a significant increase with evolving clinical state, with a tenfold difference in IgA antibodies specific to *Ps aeruginosa* between the patients with the worst and the best clinical score. Titres of IgM and IgE antibodies specific to *Ps aeruginosa* were raised in 17 (30%) of the patients but did not correlate with clinical state. There was a moderately significant correlation ($p<0·05$) among IgG, IgA, and IgM antibodies specific for *Ps aeruginosa* and serum concentrations of IgG, IgA, and IgM ($r=0·44$, 0·31, and 0·46, respectively).

Class specific antibodies to *Ps aeruginosa* could be

Table 1 *Mean (SD) serum concentrations of immunoglobulins in patients with cystic fibrosis and number of patients (%) with raised concentrations*

Immunoglobulin	*Shwachman score*			*p Value*
	<55 (n=14)	*55–70 (n=18)*	*≥70 (n=25)*	
IgG:				
Mean (SD) concentration (g/l)	22·03 (16·52–29·51)	18·08 (14·08–23·21)	12·61 (8·54–18·63)	<0·001
No (%) of patients with raised concentration	10 (71)	13 (72)	7 (28)	
IgA:				
Mean (SD) concentration (g/l)	4·11 (2·57–6·58)	2·44 (1·44–4·15)	1·37 (0·73–2·57)	<0·001
No (%) of patients with raised concentration	10 (71)	4 (22)	2 (8)	
IgM:				
Mean (SD) concentration (g/l)	1·83 (1·14–3·11)	1·76 (1·07–2·90)	1·18 (0·40–3·44)	0·262
No (%) of patients with raised concentration	10 (71)	14 (78)	19 (76)	
IgE:				
Mean (SD) concentration (kU/l)	85 (15–478)	219 (49–982)	54 (14–211)	0·032
No (%) of patients with raised concentration	4 (31)	11 (61)	5 (22)	

detected in the polyethylene glycol precipitate in some patients. Significantly higher titres of IgG and IgA antibodies to *Ps aeruginosa* were found in the groups with the worse clinical states. In most of the samples containing circulating immune complexes, we found raised titres of antibodies to *Ps aeruginosa* (tables 4 and 5).

Ps aeruginosa was not isolated from the sputum of eight patients. These were all in group 3 (Shwachman score 70 or more) and their mean age was 7·7 years (range 4·2–15·6), which is less than the mean age of the whole group. Three of these patients had raised titres of IgA antibodies to *Ps aeruginosa* and one of them had raised titres of IgE antibodies to *Ps aeruginosa*. The subject who had *S pneumoniae* in his sputum also had raised serum concentrations of IgM circulating immune complexes, and raised titres of IgM to *Ps aeruginosa* and IgM antibodies to *Ps aeruginosa* were found in the circulating immune complexes. None of the other subjects who did not have *Ps aeruginosa* in their sputum had raised circulating immune complexes.

Table 2 *Mean (SD) concentrations of class specific circulating immune complexes expressed as arbitrary units and number (%) of patients with raised concentrations*

Class specific circulating immune complexes containing	*Control population*	*Shwachman score*			*p Value*
		<55 (n=14)	*55–70 (n=18)*	*≥70 (n=25)*	
IgG.					
Mean (SD) concentration	7 5 (5 8–9·9)	76·7 (33 1–177 7)	55 1 (22 2–137·0)	26 3 (12 8–54 1)	0 030
No (%) of patients with raised concentration		10 (75)	12 (67)	3 (10)	
IgA:					
Mean (SD) concentration	3 2 (1·7–6 2)	8 41 (2 4–29 4)	4·8 (1 7–13 7)	1·8 (0·5–5·9)	<0 001
No (%) of patients with raised concentration		7 (50)	4 (22)	2 (8)	
IgM·					
Mean (SD) concentration	5·0 (2 7–9 0)	10·8 (4 8–24 3)	11·4 (5·5–23 6)	8·2 (4·1–16 8)	0·302
No (%) of patients with raised concentration		5 (36)	7 (39)	4 (16)	

Table 3 *Mean (SD) titres of antibodies specific for Ps aeruginosa expressed as arbitrary units and number (%) of patients with raised titres*

Titres of antibodies specific for Ps aeruginosa	*Control population*	*Shwachman score*			*p Value*
		<55 (n=14)	*55–70 (n=18)*	*≥70 (n=25)*	
IgG					
Mean (SD) titre	130 (98–174)	1588 (523–4817)	428 (137–1339)	176 (43–713)	<0 001
No (%) of patients with raised titres		13 (93)	13 (72)	12 (48)	
IgA.					
Mean (SD) titre	8 (4–16)	757 (230–2490)	143 (35–584)	61 (12–299)	<0 001
No (%) of patients with raised titres		14 (100)	16 (89)	18 (72)	
IgM					
Mean (SD) titre	88 (45–174)	148 (63–351)	137 (59–317)	124 (62–250)	0·697
No (%) of patients with raised titres		5 (36)	5 (28)	7 (28)	
IgG					
Mean (SD) titre	11 (5–25)	40 (14–117)	48 (12–202)	54 (23–213)	0 638
No (%) of patients with raised titres		3 (21)	7 (39)	7 (28)	

Table 4 *Mean (SD) titres of antibodies specific for Ps aeruginosa in the polyethylene glycol precipitate expressed as arbitrary units*

Titres of antibodies specific for Ps aeruginosa	*Shwachman score*			*p Value*
	<55 (n=14)	*55–70 (n=18)*	*≥70 (n=25)*	
IgG	4·9 (0·9–25 5)	2 1 (0·4–10 1)	1 1 (0 3–3·5)	0 014
IgA	2 2 (0 7–7·2)	0 9 (0 4–2·0)	0 5 (0 2–1 2)	<0 001
IgM	3·3 (0·8–14·2)	4·9 (1 7–14 2)	2·6 (0·4–16 6)	0·590

Table 5 *Number of patients with circulating immune complexes and raised titres of antibody to Ps aeruginosa in the polyethylene glycol precipitate*

Antibody specific for Ps aeruginosa	*Shwachman score*			*Total No*
	≤55	*55–70*	*≥70*	
IgG	4/6	1/4	0/1	5/11
IgA	5/7	0/4	1/2	6/13
IgM	3/5	3/7	2/4	8/16

Table 6 *Significance of correlations among respiratory function tests and other measurements*

Measurement	*FEV₁*		*Total gas volume*		*Residual volume*	
	Correlation coefficient	*p Value*	*Correlation coefficient*	*p Value*	*Correlation coefficient*	*p Value*
Shwachman score	0·70	<0·001	−0·57	<0·001	−0·70	<0·001
Concentration of						
IgG	−0·52	<0·001	0·34	<0·008	0·41	0·002
IgA	−0·57	<0·001	0·30	0·018	0·39	0·003
IgM	−0·24	0·044	0·05	0·36	0·07	0·315
Circulating immune complexes containing:						
IgG	−0·51	0·007	0·37	0·042	0·41	0·026
IgA	−0·51	<0·001	0·20	0·08	0·29	0·021
IgM	−0·34	0·008	0·09	0·278	0·11	0·217
Antibodies specific to *Ps aeruginosa*:						
IgG	−0·47	<0·001	0·34	0·007	0·36	0·006
IgA	−0·39	0·003	0·33	0·011	0·37	0·004
IgM	−0·15	0·142	0·23	0·058	0·24	0·046
Antibodies to *Ps aeruginosa* in circulating immune complexes:						
IgG	−0·52	<0·001	0·21	0·078	0·24	0·048
IgA	−0·60	0·001	0·30	0·020	0·34	0·008
IgM	−0·27	0·031	0·10	0·257	0·14	0·176

FEV_1 and residual volume correlated well with the Shwachman score (table 6). Significant correlations were also found between FEV_1, total gas volume, and residual volume on the one hand, and concentrations of immunoglobulins and circulating immune complexes, and titres of antibodies to *Ps aeruginosa* on the other.

Discussion

In this group of patients with cystic fibrosis colonisation of the respiratory tract with *Ps aeruginosa* was detected in 49 (86%). Only in eight patients in group 3 could *Ps aeruginosa* not be detected in the sputum. Most centres treating patients with cystic fibrosis have reported similar isolation rates, particularly in patients with advanced disease.[13]

There have been several reports of the association between serum immunoglobulin concentrations and clinical state in patients with cystic fibrosis.[14 15] Most reports have focused on IgG, and studies concerning total IgM or IgA or concerning antibodies specific to *Ps aeruginosa* are scarce. There have also been various reports about the presence and importance of circulating immune complexes, but class specific circulating immune complexes have seldom been studied in patients with cystic fibrosis.

As in previous studies, significant differences in total immunoglobulin concentrations among the three clinical groups were found, except for IgM; the IgM concentrations were equally raised in the three groups. In a study by Turner *et al* an association was also detected between high concentrations of IgG and IgA (but not IgM) and recurrent infection.[14] On the other hand, low concentrations of immunoglobulins have been reported to be associated with milder lung disease and slower progression of pulmonary impairment.[15] None of our patients had hypogammaglobulinaemia. Many other studies have shown variable rises in immunoglobulin concentrations in serum samples from patients with cystic fibrosis.[16] Twenty one (37%) of our subjects had raised concentrations of IgE. This confirms the finding of Wallwork and McFarlane who found raised concentrations of IgE in 32% of their patients.[16] Several other workers have reported raised total IgE and raised titres of allergen specific IgE antibodies in association with positive skin prick tests in patients with cystic fibrosis.[14 17] Turner *et al* reported a clear association between IgE concentrations and the number of recent respiratory tract infections.[14] Furthermore, it has been shown that recurrent infection and inflammation of the bronchial tree lowers the threshold of irritant receptors leading to bronchial hyperreactivity.[18]

Though raised concentrations of circulating immune complexes have been described,[1] the presence of class specific circulating immune complexes has not been well studied in patients with cystic fibrosis. In our study, concentrations of IgG and IgA containing circulating immune complexes were highest in patients with advanced disease, whereas concentrations of IgM containing circulating immune complexes were not associated with worsening of the clinical state. Whether circulating immune complexes containing IgG or IgA are actively concerned in the progression of the lung disease needs to be elucidated. That circulating immune complexes containing IgG and IgA could be partly responsible for the progression of the disease and not solely reflecting the duration of colonisation with *Ps aeruginosa* is suggested by the finding of immune complex deposition in the respiratory tracts of patients with cystic fibrosis,[1] and by the development of cutaneous vasculitis in some patients with cystic fibrosis. Another indication of the pathogenic role of these immune complexes comes from the in vitro experiments that showed a release of mediators from inflammatory cells by circulating immune complexes containing IgG or IgA in patients with cystic fibrosis [19] Recent clinical studies also suggest that circulating immune complexes are an independent risk factor for death from cystic fibrosis, and that they are also associated with poor prognosis. Other workers, however, have suggested that the concentration of circulating immune complexes cannot be used as markers for infectious exacerbations, but have to be considered as indicators of the chronic nature of the disease

Antibodies specific to *Ps aeruginosa* were found in most patients, with significant differences in IgG and IgA antibodies specific to *Ps aeruginosa* among the three groups The highest titres were found in patients with the worst clinical state. These data confirm the results of other studies that showed that high titres of IgG antibody specific to *Ps aeruginosa* were associated with poor clinical state, and that it is a sensitive and specific marker for the severity and progress of infection with *Ps aeruginosa* in patients with cystic fibrosis.[20] Titres of IgA antibodies specific to *Ps aeruginosa* have not been widely studied and it is therefore interesting that they were the most often raised, even in patients who were clinically well—18 out of 25 (72%) of the patients with less severe disease had raised titres of IgA antibodies specific for *Ps aeruginosa*—or in patients without *Ps aeruginosa* in their sputum samples (three of eight). Because titres of IgA antibodies to *Ps aeruginosa* were significantly lower in serum samples from control subjects than in those from patients with good or excellent clinical state, and because these titres increase with the severity of the disease, it might be that IgA antibodies to *Ps aeruginosa* are specific and sensitive detectors of infection by *Ps aeruginosa* in young children with cystic fibrosis. Furthermore they could indicate previous infection with *Ps aeruginosa* in patients with cystic fibrosis who were not currently growing *Ps aeruginosa* in their sputum.

The highest titres of IgA antibodies to *Ps aeruginosa* in circulating immune complexes were found in the patients with the most progressive disease, there being significant differences among the three clinical groups. Antigens and antibodies to *Ps aeruginosa* have been detected in circulating immune complexes by a number of workers, and have been associated with colonisation by *Ps aeruginosa* and advanced disease. Moss and Hsu showed that patients with cystic fibrosis who had increased concentrations of circulating immune complexes, these complexes contained IgG antibody to *Ps aeruginosa*.[5] Other authors showed that circulating immune complexes contained antibody to *Ps aeruginosa* lipopolysaccharide and had endotoxin activity.[4]

In conclusion it seems that IgA is a sensitive marker of colonisation by *Ps aeruginosa* in patients with cystic fibrosis. Concentrations of total IgA, specific circulating immune complexes containing IgA, and IgA antibody titres to *Ps aeruginosa* are closely associated with the clinical progression of cystic fibrosis as judged by the Shwachman score and lung function tests. The use of IgA antibody to *Ps aeruginosa* as an early marker of colonisation by *Ps aeruginosa* or as an indicator of previous infection with *Ps aeruginosa* in patients with cystic fibrosis needs further study but could be important, particularly in young children from whom it is difficult to collect sputum for culture.

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Faecal chymotrypsin concentrations in neonates with cystic fibrosis and healthy controls

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SUMMARY Specimens of meconium and random stools were collected sequentially from 25 healthy newborn babies over the first 8–14 days of life. The stool chymotrypsin concentrations increased from birth to a maximum at 4 days of age and then fell again over the next four days. The lowest individual stool concentrations either side of the four day peak were both, coincidentally, 120 μg/g stool. In a second group of 22 newborn babies suspected of meconium ileus and later confirmed to have cystic fibrosis, faecal chymotrypsin concentrations were all appreciably reduced. In eight babies, also with suspected meconium ileus but with negative sweat tests, chymotrypsin concentrations were within the healthy newborn range.

Measuring faecal chymotrypsin concentrations is a reliable procedure for identifying pancreatic exocrine insufficiency in the newborn.

Intraduodenal tests of pancreatic exocrine function are invasive, technically difficult, and expensive and many alternative tests have been suggested. One of the alternatives proposed, the measurement of pancreatic proteolytic enzymes in faeces, has produced several validation studies in adults showing significant positive correlations between pancreatic proteolytic enzyme secretion and faecal excretion.[1-3] A more recent study in children produced a highly significant positive correlation between the pancreatic chymotrypsin secretion rate into the duodenum after pancreozymin stimulation and the mean faecal chymotrypsin concentration of three random stools.[4] It also showed, using a single random stool, that chymotrypsin concentration was profoundly depressed or absent in 46 children with clinical malabsorption due to cystic fibrosis.

Many children with cystic fibrosis are now identified in the neonatal period but the diagnosis may not be confirmed by sweat testing for several weeks because of the poor sweat excretion rate of the neonate. Until that time the diagnosis must remain presumptive but the demonstration of pancreatic exocrine insufficiency would be strong corroborative evidence in favour of the diagnosis and would provide a sound basis for the immediate start of pancreatic enzyme replacement. Only one detailed study has been reported on faecal chymotrypsin excretion in healthy children in this age group[5] and there are no similar data on chymotrypsin excretion in the newborn with cystic fibrosis. In this report we present a reference range for random stool chymotrypsin concentrations in the healthy neonate and data from a second group of neonates with suspected meconium ileus, three quarters of whom were subsequently shown to have cystic fibrosis.

Patients and methods

HEALTHY NEONATES

Twenty five newborn babies were admitted to the study on delivery. Seven of the 25 babies were born preterm with gestational ages of 32–36 weeks. Five of the babies were breast fed. The remainder received formula at intervals of four hours throughout the day or more often in the case of the lower birthweight babies. All formula fed babies received body weight related milk volumes. Birth weights ranged from 1720 to 3840 g. Four of the term babies and two of the preterm babies had birth weights below the 10th centile for the gestational age.

Random meconium and stool samples were collected at least every other day from each baby during their stay in the maternity unit. A total of 156 samples were obtained, the earliest specimen being collected at three hours after birth, and the latest at 336 hours (14 days). The number of stools collected from the individual baby varied, the smallest number collected from a single baby being four samples and the largest number eight (median six). The collection period covered the transition from the excretion of dark green-brown pigmented meconium to the bright yellow pigmentation of faeces. Specimen pigmentation was recorded.

NEONATES WITH SUSPECTED MECONIUM ILEUS

A single specimen of faeces (n=26) or colostomy fluid (n=4) was collected from a second group of 30 newborn babies between 3 and 21 days of age. The babies in this group had intestinal obstruction with clinical or radiological features, or both, suggesting meconium ileus. Specimens were obtained in each case by normal bowel action. In two babies in whom the initial chymotrypsin concentration was high in relation to the rest of the group, but still clearly subnormal when compared with the healthy neonates, follow up specimens were collected.

ANALYTICAL METHODS

Stool and colostomy fluid specimens (1–2 g) were collected in polystyrene Falcon stool containers and stored at −20°C until analysed. Specimens from healthy neonates were accumulated until the baby went home so that all stools from a given baby were analysed in the same analytical batch. All analyses were completed within 14 days of collection.

Chymotrypsin activity was measured by the method of Haverback *et al*.[6] Details of the procedure, together with method performance data, have been published previously.[4]

STATISTICAL EVALUATION

All statistical evaluations were non-parametric. The degree of association between two measurements and its significance was determined using Spearman's rank correlation coefficient. The significance of differences between groups was determined using the Mann-Whitney U test.

Results

HEALTHY NEONATES

Individual stool chymotrypsin values (fig 1)

The random stool data from all 25 babies were grouped into 24 hour periods from birth. Chymotrypsin concentrations increased rapidly over the first 48 hours of life, then increased more slowly, reaching a peak in the fourth 24 hour period. Concentrations then fell back again, over the next four 24 hour periods, to the range seen in the first 24 hours of life. The peak was well defined in some babies but less so in others, presumably due to the random nature of the stool collection. The median chymotrypsin concentration of specimens passed in the first 24 hours after birth was 290 μg/g stool and the lowest concentration was 120 μg/g stool. The median value increased to 725 μg/g stool for the fourth 24 hour period with the lowest individual value being 305 μg/g stool. Twenty four hour median values then declined over the remainder of the study period to about 200 μg/g. The lowest value observed in this latter period was again, coincidentally, 120 μg/g stool.

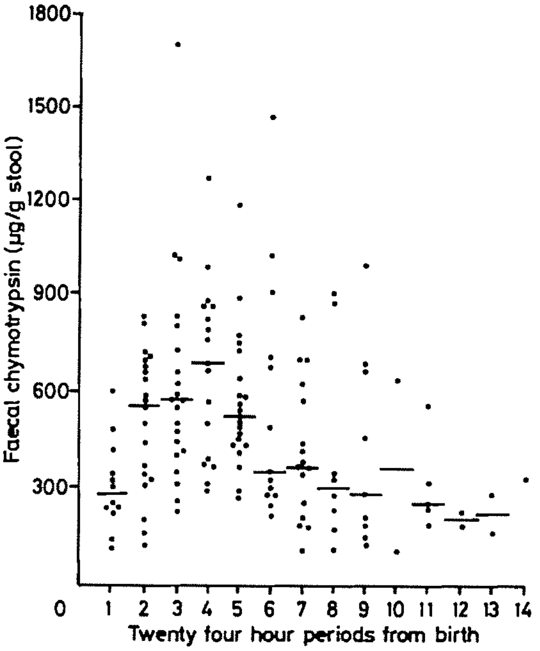

Fig 1 *Random stool chymotrypsin concentrations in the 25 healthy babies. Results are grouped into 24 hour periods after birth. The horizontal bars show the median value for each interval*

The overall range of individual stool chymotrypsin activities from all 25 babies, over the period of 3–336 hours (14 days), was 120–1680 μg/g stool. The results from one baby were excluded from this range. Initial values in this baby were unexceptional. They then increased to very high values, (1880, 2020, and 1840 μg/g stool) during the second, third, and fourth 24 hour periods, falling finally to values similar to the rest of the group. A three month follow up on this baby did not disclose any abnormality.

The individual stool values from the seven preterm babies tended to be lower than the term babies, the highest preterm value being 1264 μg/g stool. At the lower end of the range values were similar with none of the preterm baby values falling below the lower end of the term baby range.

Mean stool chymotrypsin concentrations

A mean chymotrypsin concentration was calculated for each baby using the data from stool specimens passed between birth and 8 days of age The mean values in the term babies (range 345–888, median 581 μg/g stool) increased with increasing birth weight (fig 2) producing a significant positive correlation ($r=0{\cdot}643$, $p<0{\cdot}01$). The mean value for the baby who produced extremely high individual stool values on days 2, 3, and 4 was greater than the mean plus 3 standard deviations for the remaining 17 term babies. Data from this baby therefore was not included in the birthweight correlation (fig 2), although inclusion still produced a significant value ($r=0{\cdot}487$, $p<0{\cdot}05$).

Mean chymotrypsin concentrations in the seven preterm babies (range 262–678, median 392 μg/g stool) tended to be low with five at or below the median value for the whole group. They were not, however, significantly lower than the mean values of the term babies ($p=0{\cdot}054$). Only the lowest birthweight preterm baby had a mean value below the observed range of the term babies or a range expressed by the mean minus 2 standard deviations. Values in the light for dates babies were similar to those of the appropriate weight babies. Values for the breast fed babies were also unexceptional.

Stool pigmentation

The time of transition of specimen pigmentation varied. Yellow faecal pigmentation appeared as early as 48 hours in some babies while others produced meconium pigmented material as late as 120 hours after birth The average time for the transition occurred at around the fourth 24 hour period, coinciding with peak chymotrypsin activity

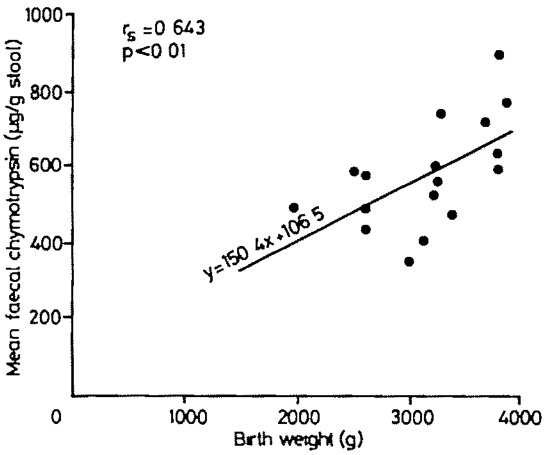

Fig 2 *Correlation of birth weight with mean faecal chymotrypsin concentration in the term babies.*

NEONATES WITH SUSPECTED MECONIUM ILEUS

The data for random stool chymotrypsin concentrations from this group in relation to the results of sweat tests done at 6 weeks of age or later are shown in fig 3.

Sweat test positive babies

In the 22 babies who had sweat electrolyte concentrations consistent with a diagnosis of cystic fibrosis, the two highest faecal chymotrypsin concentrations were 57% and 33% (68 and 48 μg/g stool) of the lowest value seen in the healthy neonates. Repeat testing in those two babies, one week after the initial observation, produced concentrations of 10% or less of the lowest normal value (12 and 8 μg/g stool). In the remaining 20 babies who had a positive sweat test, faecal chymotrypsin concentrations were 17% or less (median overall 6%) of the lowest value in the healthy neonates. Activity was not detectable in seven.

In one of the two babies producing the high chymotrypsin concentrations, seven repeat observations were made between 3 and 16 days. The initial value at 3 days was 16 μg/g stool, the concentration rose to 48 μg/g on day 5 then decreased to nil by day

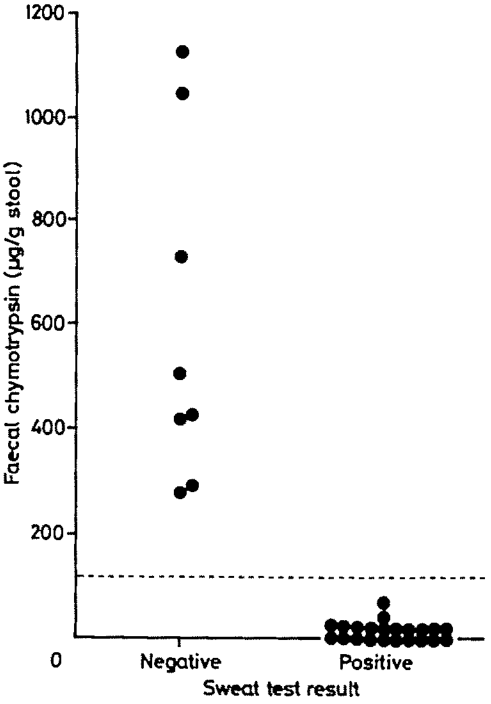

Fig 3 *Single random stool chymotrypsin concentrations in babies either negative or positive for the sweat test. The broken line shows the lower limit of the observed range in the healthy neonates*

13. This pattern was similar to that shown by the healthy neonates but at a much lower concentration level

In the stool specimens from the babies with a positive sweat test that contained detectable concentrations of chymotrypsin, the 14 specimens passed before 10 days of age had significantly higher chymotrypsin concentrations ($p=0 \cdot 025$) than the 10 specimens passed between 10 and 20 days.

Sweat test negative babies

In the eight babies whose sweat electrolytes were normal, the chymotrypsin concentrations, including the single colostomy specimen in this group, were well within the faecal chymotrypsin normal range, the lowest value being 275 µg/g stool.

Discussion

In the healthy neonates faecal chymotrypsin concentrations varied with the age of the baby over the first 8 days of life. The lower limit of the range also varied over the same period but the lowest concentration at any time during the study was 120 µg/g stool and this has been adopted as the lower limit of the observed range for healthy neonates.

The lower mean faecal chymotrypsin concentrations in the preterm babies were in accord with intraduodenal observations already reported that pancreatic exocrine secretory activity in the preterm baby is reduced compared with the term baby.[7] [8] Pancreatic function has not been shown to be different in light for dates or breast fed babies and the faecal chymotrypsin concentrations were not obviously different in babies in either category in this study.

The higher faecal chymotrypsin concentrations in the higher birthweight babies suggested greater pancreatic activity. This may have been an inherent feature but it may also have been due to the feeding regime, the heaviest babies receiving almost twice the protein intake of the lightest. Large increases in protein intake increase intraduodenal enzyme concentrations.[9]

The very high values seen in one of the healthy neonates remain unexplained. They may have been normal but appeared otherwise because of the relatively small size of the group investigated. Alternatively, they may have been the result of a brief phase of greatly increased pancreatic activity. Further work with this non-invasive test is indicated. It may produce information about the physiological modulation of pancreatic function that would be unobtainable by intraduodenal testing.

Little data on neonatal faecal chymotrypsin concentrations have been published for comparison. Mullinger and Palasi also found increasing faecal chymotrypsin concentrations during the first 3 days of life, but, unlike those reported in our data they rose further on days 6 and 7.[5] In a more recent study reporting chymotrypsin concentrations in the stool aqueous phase of the preterm neonate, concentrations decreased between 1 and 2 weeks of age.[10] Direct comparison with our data from whole stool homogenate is difficult as most of the chymotrypsin activity was firmly bound to the solid phase. The decreasing activity described in the 2nd week of life and the lower concentration at this age, however, compared with older infants, is consistent with our findings.

A similar pattern of changing concentration has been reported for pancreozymin stimulated duodenal enzymes in the neonate,[7] for gastric acid concentration,[11] and for plasma gastrin and enteroglucagon concentrations.[12] This coinciding, similar surge of endocrine and exocrine activity in the first few days of life appears to be a part of the initial endocrine-exocrine response to the introduction of enteral feeding. The early high gut enzyme concentration may result in more efficient mobilisation and elimination of the meconium, the peak faecal enzyme concentration at 4 days of age coinciding with the change from meconium to faecal pigmentation of the stools.

The duodenal-faecal enzyme relation in the healthy neonate appears to be sufficiently close for the subtle perinatal changes in pancreatic function to be shown by faecal chymotrypsin measurements and the latter may therefore be useful in other physiological or nutritional studies.

Chymotrypsin concentrations were grossly subnormal in all 22 babies subsequently shown to have cystic fibrosis. We do not have reference values for chymotrypsin concentrations in colostomy fluid but the concentrations in the three colostomy fluid samples from babies with a positive sweat test and the single colostomy fluid from a baby with a negative sweat test were in the same ranges as the faecal concentrations from those groups. We consider them therefore to be of similar importance to the faecal measurements in this context.

The two highest chymotrypsin concentrations in the babies with cystic fibrosis were produced at ages of 5 and 6 days respectively, that is, close to the time of peak concentration in the healthy neonates. On repeat testing a few days later the concentrations had fallen to the very low concentrations more characteristic of cystic fibrosis. Where intermediate values are found therefore, particularly in the first week of life, repeat testing is essential.

The full clinical value of faecal chymotrypsin measurement in the neonate remains to be determined. The concentrations seen in the babies with cystic fibrosis in this study indicate gross pancreatic exocrine insufficiency and concentrations presumably would be similar in the other inborn errors characterised by profound pancreatic exocrine insufficiency, although the non-cystic fibrosis disorders are very rare. Absence of chymotryptic activity may also result from a functional or anatomic defect preventing transit, or extremely rarely, enterokinase deficiency. Where cystic fibrosis is suspected, however, absence of faecal chymotrypsin would be a strong indicator in favour of the diagnosis and such information would be available several weeks in advance of a sweat test result. Despite its value in this particular context, however, it must be remembered that faecal chymotrypsin is a measure of pancreatic function and not a screening test for cystic fibrosis.

Faecal enzyme measurements are likely to give a less accurate assessment of pancreatic exocrine activity than the more direct intraduodenal tests. This study and our earlier investigations have shown, however, that the duodenal-faecal relation is sufficiently close for many of the questions asked about pancreatic function in the neonate to be answered by faecal studies.[4] Compared with intraduodenal testing, faecal chymotrypsin measurements have the additional advantages of being non-invasive, rapid, simple, inexpensive, and repeatable as often as required.

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HLA type, islet cell antibodies, and glucose intolerance in cystic fibrosis

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SUMMARY Impaired glucose tolerance, assessed by a raised glycated haemoglobin (HbA_1) concentration, was found in 24 (39%) out of 61 patients with cystic fibrosis with an age range of 1–23 years. No correlation between age and HbA_1 concentration was found indicating that factors other than progressive pancreatic fibrosis may be important in the aetiology. HLA typing, islet cell antibodies, and autoantibody screen were completed. Eighteen (75%) out of 24 patients with cystic fibrosis who had an impaired glucose tolerance had HLA-DR3 or HLA-DR4 antigens compared with 23 (62%) out of 37 patients with normal glucose tolerance. Islet cell antibodies were present in seven (15%) out of 46 patients with cystic fibrosis; the prevalence in a normal population is 0·5%. Five (25%) of the 20 patients with a raised HbA_1 concentration were positive for islet cell antibodies compared with two (8%) out of the 26 with normal glucose tolerance. Six (86%) out of seven patients who were positive for islet cell antibodies had HLA-DR3 or HLA-DR4 antigens. There was no general autoantibody production. Islet cell antibodies may play a part in the development of glucose intolerance in some patients with cystic fibrosis by being produced in those who are genetically predisposed as part of an immune response to damaged pancreatic tissue.

The incidence of insulin dependent diabetes in patients with cystic fibrosis is reported to be 1–10%[1-3]; this is many times the incidence in a normal population.[4] Glucose intolerance occurs in 8–75%.[1] Early studies suggested that glucose intolerance develops in patients with cystic fibrosis secondary to pancreatic damage after exocrine pancreatic disease rather than in association with juvenile onset diabetes. Increasing disruption of islet cells without decrease in islet cell number was found with increasing age, as a result of progressive pancreatic fibrosis.[5] It was proposed that the islet cell disruption led to the delayed and impaired release of insulin, leading to glucose intolerance. Immunohistochemical techniques, however, have shown a reduced islet and β cell number in patients with cystic fibrosis who have insulin dependent diabetes.[2 3 6] In addition, a lack of correlation between glucose intolerance, age, and Shwachman score has been reported.[2 7] These findings suggest that aetiological factors other than progressive pancreatic fibrosis may contribute to the development of glucose intolerance and insulin dependence.

The increased familial incidence and the association with HLA genes B8, B15, and in particular DR3 and DR4, indicates that genetic factors are important in the aetiology of type I insulin dependent diabetes.[8-11] In patients with cystic fibrosis no association has been found so far between HLA type and insulin dependent diabetes.[12]

Islet cell antibodies have been reported in a high proportion of patients with insulin dependent diabetes at diagnosis, but are less common as the duration of the disease increases.[11] The presence of islet cell antibodies may precede the development of overt symptomatology in predisposed people,[13 14] but their role in the pathogenesis is unclear. It is debatable whether they produce direct islet cell damage[15] or serve only as markers for islet cell destruction.[16] Antibodies to human pancreas have been shown in patients with cystic fibrosis[17] but the presence of islet cell antibodies has not been reported. An increased incidence of autoantibodies to smooth muscle,[18] reticulin,[19] and lung[17] and antinuclear antibodies[20] have been found in patients with cystic fibrosis.

The aim of this study was to determine possible genetic and autoimmune factors in the aetiology of glucose intolerance and insulin dependent diabetes in a group of patients with cystic fibrosis. The HLA type and presence of a variety of autoantibodies, including islet cell antibodies was investigated and related to the presence of glucose intolerance in these patients

Patients and methods

Sixty one of the 64 patients attending the clinic for cystic fibrosis at Alder Hey Children's Hospital between January and June 1985 were entered into this study. Their mean (SD) age was 9 (5·3) years, range 1–23 years. The presence of glucose intolerance was assessed at the time of recruitment by measuring the concentration of glycated haemoglobin (HbA_1). This was repeated at intervals of two to six months for a period of one year. A standard oral glucose tolerance test (1·75 g/kg glucose, maximum 75 g)[21] was completed on patients with a raised HbA_1 concentration and where possible patients with cystic fibrosis with a normal HbA_1 who were of similar age.[22] None of the patients was taking drugs that could influence glucose tolerance—for example, steroids or salbutamol—and none had acute infections at the time of the study. No patient was iron deficient on haematological assessment Blood was taken for HLA typing and autoantibody screen. The severity of cystic fibrosis was assessed using the Shwachman score,[23] pulmonary function tests, and Chrispin-Norman x ray score.[24]

HbA_1 concentrations were determined by exchange column chromatography and spectrophotometry (Biorad haemoglobin A_1, by column test) and expressed as a percentage of the total haemoglobin. The between assay standard deviation for this method was 0·68 and the coefficient of variation was 5·7%. The reference range for our laboratory is 5·3–8·8% HbA_1; representing 2SD limits of the mean of a normal paediatric population. A value of HbA_1 above 9% was considered as raised. Patients were considered to show impaired glucose tolerance if an abnormal oral glucose tolerance test or a raised HbA_1 concentration, or both, was shown.

HLA typing for A, B, and Cw specificities was carried out by a standard two stage lymphocytotoxicity microassay[25] and for DR specificities by the two colour fluorescence method.[26] Controls were healthy individuals residing in the same geographical area as the patients and included 550 typed for HLA-A, B, and Cw specificities and 232 for the DR specificities.

Plasma obtained for autoantibody tests was frozen (−20°C) before and during transport to the Middlesex Hospital for analysis. Conventional islet cell antibodies and complement fixing islet cell antibodies were determined by following a standard protocol recently used for the standardisation of islet cell antibodies.[27] The samples were tested without knowledge of the patients' details and the results confirmed by at least two independent observers. Using the same conditions for the pancreas, reagent, and incubation, the putative islet cell antibody standards currently being assessed by the immunology and diabetes workshops gave end point titres of 32 when tested 'blind' on two occasions.[28] Samples were read by two independent observers and the interassay reproducibility was one doubling dilution. Weakly positive reactions were confirmed on several human blood group O pancreases by different observers.

The autoantibody screening included gastric parietal cell antibody and a variety of non-organ specific antibodies—for example, antinuclear and mitochondrial.[29 30] Thyroglobulin and thyroid microsomal antibodies were determined by passive haemagglutination using commercial kits (Wellcome, thymune).

Ethical committee approval for the study was given and parental consent obtained.

Results

CLINICAL ANALYSIS

On entry into the study, 21 of the 61 patients with cystic fibrosis were found to have a raised HbA_1 concentration: mean 10·6%, range 9·1–17·5%. During the course of the first year a further three patients were identified with a high value. An oral glucose tolerance test was completed on 21 of these 24 patients; seven were glucose intolerant, three of these producing a diabetic response, two of whom are insulin dependent. Insulin treatment in these two patients, aged 17 and 19 years, had been started two and four years before entry into the study. Their diabetes was well controlled at this time as shown by the HbA_1 concentrations recorded (fig 1). Evidence of impaired β cell function in the 14 patients with a normal oral glucose tolerance test but raised HbA_1 concentration has been previously reported.[22] The mean (SD) HbA_1 concentration on entry to the study of the remaining 40 patients was 7·8 (0·9)%, range 5·9–8·8%; this is comparable with the 7·4 (0·94)% found in a normal population. An oral glucose tolerance test was completed on 13; all showed normal glucose tolerance. As many patients as possible were recruited. Parents were reluctant to agree to further drip siting and blood taking when their child was well when there was no evidence of glucose intolerance.

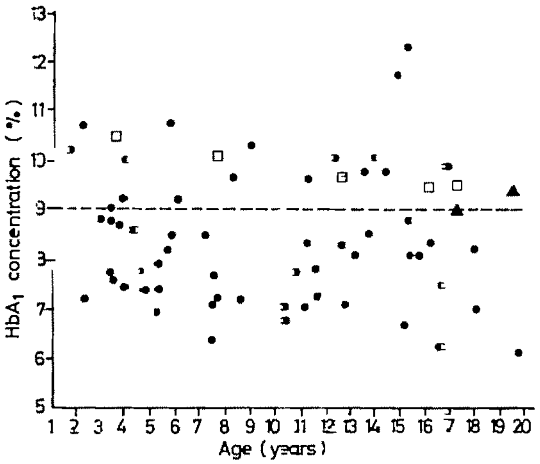

Fig 1 *Initial HbA$_1$ concentration recorded on each patient on entry to study plotted against age □=patients with confirmed glucose intolerance and ▲=insulin dependent patients. The dotted line represents the upper limit of the normal range —2SD above the mean*

No correlation was found between the concentration of HbA$_1$ and age (fig 1). Those patients shown to be glucose intolerant by the oral glucose tolerance test are indicated; the youngest was aged 3 years 8 months. No correlation was found between Shwachman score and HbA$_1$ concentration but as expected there was a significant positive correlation between age and Shwachman score.

HLA STUDIES

HLA typing was completed on all 61 patients. The relative frequency of each antigen was compared with a Liverpool population after exclusion of one of each of the five sibling pairs in the population of patients with cystic fibrosis. An increase in the frequency for HLA-A1 ($p=0·07$), HLA-A28 ($p=0·0025$), and HLA-DR6 ($p=0·026$) was seen in 56 patients with cystic fibrosis, but correction for the 42 specificities tested for showed that none of these increases was significant.

Dividing the patients with cystic fibrosis including sibling pairs, into (a) those with glucose intolerance as shown by the oral glucose tolerance test, (b) those with a raised HbA$_1$ concentration (including those in (a)) and (c) those with no evidence of glucose intolerance by either the oral glucose tolerance test or HbA$_1$, the relative frequencies of HLA-DR3 and HLA-DR4 antigen are compared with the Liverpool population (fig 2). The relative frequency of HLA-DR3 was highest in patients with cystic fibrosis who had impaired glucose tolerance although this was not significant. Eighteen (75%) of the 24 patients with cystic fibrosis who had evidence of impaired glucose tolerance had HLA-DR3 or HLA-DR4 antigen compared with 23 (62%) of the 37 patients with normal glucose tolerance.

ISLET CELL AND OTHER ANTIBODY STUDIES

The screening was completed in 46 of the 61 patients with cystic fibrosis; 20 of these had raised HbA$_1$ concentrations recorded during the one year study including six who were glucose intolerant by an oral glucose tolerance test. Repeat samples were not obtained during the study period. It was not possible to obtain appropriate blood samples on all patients. Conventional islet cell antibodies were present in seven (15%) of 46 patients (the prevalence in the normal population is 0·5%); this increase is significant, $p<0·001$. The two patients who were insulin dependent out of the six in the glucose intolerant group had islet cell antibodies in addition to three of the 14 patients with a raised HbA$_1$ concentration but a normal oral glucose tolerance test. This gives a prevalence of islet cell antibodies in those patients with cystic fibrosis who have evidence of impaired glucose tolerance of 25% (five out of 20). The remaining two patients with conventional islet cell antibodies showed no evidence of glucose intolerance; this gave a prevalence of 8% (two out of 26) in the group with no evidence of glucose intolerance. One of these had complement fixing islet cell antibodies. Further details of these patients are shown in table 1. The patients who were positive for islet cell antibodies were aged 11 to 23 years. Nineteen of the 46 patients tested for islet cell

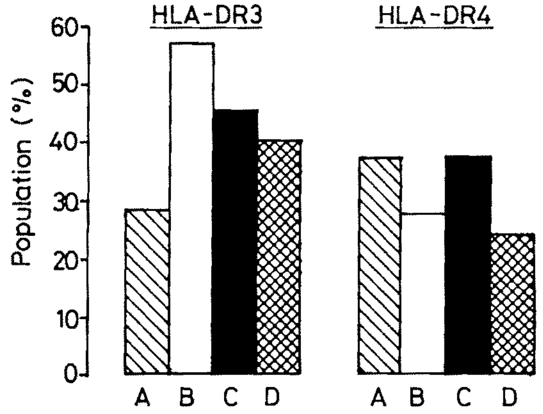

Fig 2 *HLA-DR3 and HLA-DR4 antigen frequencies in defined populations ▨=Liverpool population (n=232); □=patients with cystic fibrosis who were glucose intolerant (n=7), ■=patients with cystic fibrosis with a raised HbA$_1$ concentration, including the glucose intolerant patients (n=24), and ▩=patients with a normal oral glucose tolerance test and HbA$_1$ concentration (n=37)*

Table 1 *Details of patients with cystic fibrosis who were positive for islet cell antibodies*

Patient No	*Sex*	*Age (years)*	*Shwachman score*	*Oral glucose tolerance test*	*HbA₁ concentrations*	*HLA-A*	*HLA-B*	*HLA-DR*	*Islet cell antibodies*		*Other autoantibodies*
									Conventional	*Complement fixing*	
1*	F	17·3	45	Raised	Raised	1,11	8,35	3,4	+		
2*	F	19·6	55	Raised	Raised	1,3	8,35	3,6	+		
3	F	14·6	70	—	Raised	2,28	35,40	4	+		
4	F	14·0	90	—	Raised	1,28	8	3,6	+		
5	M	15·2	55	Normal	Raised	2,11	40	5,6	+		Antithyroid microsomal haemagglutinin antibodies × 10^2
6	M	11·3	50	Normal	Normal	3,28	8,17	3,7	+	+	
7	M	23·5	40	—	Normal	3	15,35	4	+		

*Insulin dependent

antibodies were in this age group giving an incidence of 37% (seven out of 19). The mean (SD) Shwachman score (58 (17)) for patients with islet cell antibodies did not differ significantly from patients without (65 (18)) in this age group or with the glucose intolerant patients (mean 62 (16)); this indicates that they did not have more severe clinical disease. Six (85%) out of seven patients who were positive for islet cell antibodies had HLA-DR3 or HLA-DR4 antigen. Only one patient had other autoantibodies present in addition to islet cell antibodies (patient 5, table 1).

The results of the HLA typing and autoantibody tests in the patients shown to be glucose intolerant by an oral glucose tolerance test are shown in table 2. The ages ranged from 3·6–19·6 years. Two of these patients (as discussed earlier) had islet cell anti-bodies detected and only one antinuclear antibodies.

There was no family history of insulin dependent diabetes in the patients with cystic fibrosis in this study, and there were no sibling pairs in the group who were positive for islet cell antibodies or were glucose intolerant. Maturity onset diabetes developed in one grandparent of two patients (patients 5 and 6, table 1).

Three patients had diffuse antinuclear antibodies, an overall prevalence of 7% (three out 46), and one in addition had parietal cell antibodies. Two of these had mild lung disease as assessed by Shwachman score, lung function tests, and scores on chest radiography.

Discussion

Evidence of impaired glucose tolerance was found in 39% (24/61) of patients with cystic fibrosis as assessed by a raised HbA_1 concentration. Factors that could produce glucose intolerance in these patients were excluded. There was no evidence of penicilloylated haemoglobin causing falsely raised HbA_1 concentrations.[31] All patients were given prophylactic antibiotics; 40 had HbA_1 concentrations within the normal range. Patients with raised HbA_1 had impaired and delayed C peptide response to oral glucose loading indicating impaired β cell function.[22] Two patients with cystic fibrosis developed insulin dependent diabetes, an incidence of 3%. The increased incidence of glucose intolerance and diabetes found in this study is in accordance with the findings of others.[1–3] The reported lack of correlation between age and glucose intolerance was confirmed,[2 7] indicating that aetiological factors other than pancreatic islet cell disruption with progressive fibrosis may be important in the development of glucose intolerance and diabetes in some patients with cystic fibrosis.

Table 2 *Details of patients with cystic fibrosis who were glucose intolerant (by oral glucose tolerance test)*

Patient No	*Sex*	*Age (years)*	*Shwachman score*	*HLA-A*	*HLA-B*	*HLA-DR*	*Islet cell antibodies*		*Other autoantibodies*
							Conventional	*Complement fixing*	
8	M	3·6	80	3,11	13,18	3,7	–	–	
9	F	9·1	75	1,9	7,8	2,3	–	–	
10	F	13·3	80	3,9	7	5,6	–	–	
11	M	16·2	50	10,11	18,27	2,4	–	–	Antinuclear antibody diffuse
12	M	17·5	50	1,9	5,12	5,6	–	–	
1*	F	17·3	45	1,11	8,35	3,4	+	–	
2*	F	19·6	55	1,3	8,35	3,6	+	–	

*Insulin dependent.

Genetic linkage between the cystic fibrosis and a diabetogenic associated gene is unlikely as there is no increased incidence of cystic fibrosis in families with insulin dependent diabetes. Schwarz *et al* reported the results of HLA typing on six patients with cystic fibrosis who developed diabetes mellitus.[12] Only two of these patients had HLA-DR3 or HLA-DR4 antigens in contrast with 53 out of 55 children with insulin dependent diabetes also included in the study. The high incidence of HLA-DR3 or HLA-DR4 antigens in this latter group is consistent with the strong association between these alleles and insulin dependent diabetes reported elsewhere.[8] The relative risk of developing diabetes is increased five times in any individual with the inheritance of HLA, DR3, or DR4 phenotype.[8] The evidence suggests that the genes which confer susceptibility to the development of insulitis are in linkage disequilibrium with HLA-DR3 or HLA-DR4, although recent evidence suggests that the direct involvement of the DQ β gene at an adjacent locus may be more significant.[32] We found an increase in HLA-DR3 antigen in the patients with cystic fibrosis in this study particularly in the patients shown to be glucose intolerant. This was not significant, however, possibly because of the small number of patients in this study. Both of the patients with cystic fibrosis who had insulin dependent diabetes had HLA-B8 and HLA-DR3 in addition to islet cell antibodies. Their diabetes, however, has followed the course characteristic of patients with cystic fibrosis rather than juvenile onset diabetes. Neither had a family history of diabetes and no episodes of ketoacidosis have occurred despite recurrent chest infections. In addition the insulin dosage required to obtain reasonable diabetic control was moderate with insulin dosages of 0·8 and 1·3 units/kg/24 hours.

Islet cell antibodies were detected in seven out of 46 (15%) of the patients with cystic fibrosis investigated, six of whom had HLA-DR3 or HLA-DR4 antigens. All were older than 11 years giving an incidence in the 11–23 year age group of 37%. Dividing the patients into two groups, five out of 20 (25%) patients with cystic fibrosis who had evidence of impaired glucose tolerance as assessed by HbA$_1$ were positive for islet cell antibodies compared with two out of 26 (8%) of those with normal glucose tolerance. This difference is not significant possibly because of the small number of patients studied but it shows an interesting trend. It is known that the presence of islet cell antibodies may precede the development of glucose intolerance by a number of years. These patients will be studied prospectively to determine the final outcome.

The incidence of islet cell antibodies in a normal population detected in our laboratory is 0·5% comparable with that reported by others (0·5% of 434 control subjects).[11] In patients with insulin dependent diabetes the prevalence of islet cell antibodies is reported to be dependent on the duration of the diabetes. The presence of islet cell antibodies more than five years after diagnosis was positively correlated with the presence of HLA-A1 and HLA-B8[11]; these were present in both our diabetic patients. There is evidence that the onset of type I diabetes is slow and develops over several years.[13 14 33] β Cell function may deteriorate gradually during this time with clinical presentation possibly precipitated by a viral infection.[34] The increased incidence of islet cell antibodies in our patients with cystic fibrosis may reflect that in those patients who have a genetic predisposition an autoimmune response may be mounted to damaged pancreatic tissue with the production of antibodies to islet cells. This may result in further β cell destruction. Evidence of impaired β cell function was present in five out of seven (71%) patients positive for islet cell antibodies at the time of the study. The production of these antibodies was not seen to be part of a generalised autoantibody response to increased antigenic stimulation as only one patient positive for them had other autoantibodies present.

In conclusion, evidence of impaired glucose tolerance was found in 24 out of 61 (39%) of the patients with cystic fibrosis who were studied. There was no correlation with age suggesting that factors other than increasing pancreatic fibrosis may be responsible for impaired islet cell function. An increased prevalence of islet cell antibodies was found in the population of patients with cystic fibrosis particularly those with evidence of impaired β cell function. We postulate that islet cell antibodies may play a part in the development of glucose intolerance in a proportion of these patients, being produced in genetically predisposed individuals as part of an autoimmune response to damaged pancreatic tissue.

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Outcome after antenatal diagnosis of upper urinary tract dilatation by ultrasonography

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SUMMARY A prospective study was carried out during 1986 to find out the incidence of fetal renal tract anomalies in 3228 pregnant mothers delivered in one hospital. Ultrasound examination of the fetus was performed as part of the routine antenatal assessment at 16–20 weeks' gestation, and later examinations were done if there were obstetric indications. Fetuses with any degree of dilatation of the renal pelvis or other renal tract anomalies were followed up with serial ultrasound examinations in utero and then postnatally at 6 days and 6 weeks of age, or earlier if indicated.

No renal tract anomalies were detected before 28 weeks' gestation, but of 761 fetuses examined later, 62 had dilatation of the renal pelvis not associated with overdistended bladders, and one fetus was anephric. After birth 10 of these infants (16%) were found to have pronounced renal tract abnormalities. Three who had associated serious congenital abnormalities died, five infants had obstruction of the pelviureteric junction, and two infants had vesicoureteric reflux. Antenatal ultrasonographic examination after 28 weeks identified pronounced renal tract abnormalities in asymptomatic infants with a frequency of 9·2/1000 births (seven of 761) thus permitting early treatment and reducing the incidence of late complications.

The development of ultrasound examination of the fetus has resulted in the identification of many fetal abnormalities. In particular, abnormalities of the fetal urinary tract are being recognised more often, as hydronephrotic and cystic lesions are easily seen on ultrasonography and oligohydramnios is an indication for maternal scanning. If serious fetal urinary tract abnormalities are diagnosed they are reliable indicators of urinary tract disease in the infant.[1–7]

In order to identify what proportion of minor abnormalities of the fetal renal pelvis progressed to pronounced hydronephrosis and renal tract disease in the postnatal period, we studied their occurrence and natural history. At this hospital ultrasound examinations are performed routinely on all pregnant women, usually at 16–20 weeks' gestation or on first presentation to the antenatal clinic, and later examinations are done if there are obstetric indications. All the infants included in this study were delivered at one obstetric hospital in the year 1986.

We report the outcome of patients with upper urinary tract dilatation not associated with an overdistended bladder that was diagnosed antenatally and in the absence of other renal lesions, such as cystic dysplasia.

Patients and methods

There were 62 patients in whom prenatal ultrasonographic diagnosis of unilateral or bilateral dilatation of the renal pelvis was made. All ultrasound examinations were performed with real time ultrasound equipment using a 3·5 MHz transducer. The fetal anatomy was carefully screened by the staff radiologists. Measurements were taken of the biparietal diameter, the abdominal diameter, and the length of the fetal limbs. The kidneys and urinary bladder were localised and morphology and size were noted. The examination before 20 weeks' gestation was intended to assess gestational age and the presence of more than one fetus, and also to detect fetal malformations. Those women who presented late for booking were scanned at their first visit to the clinic. There were no further routine ultrasound examinations done, but late scans were done when clinically indicated to assess fetal growth and placental site, or for other obstetric reasons.

Before 30 weeks' gestation collecting systems were seldom visible as more than echolucent slits; any that were more obvious were regarded as suspicious and were monitored by serial sonograms. A visible ureter was regarded as abnormal. After 30 weeks' gestation a visible ureter was still regarded as abnormal. Fluid clearly visible in a collecting system unilaterally was also considered abnormal and monitored by serial sonograms. Bilateral prominence of the collecting system was assessed subjectively. If the width of a collecting system measured in the anterior posterior diameter was similar to its length, abnormal dilatation was a possibility and follow up studies were done.

The maximum length of each collecting system was measured and recorded in an attempt to establish base line values. This method differs from other recently published studies in which the anterior posterior diameter was chosen.[8–10] We chose the length because it is easier to measure, and is more likely to reflect abnormalities of the renal infundibula or calyces, or both. The amniotic fluid was evaluated qualitatively as polyhydramnios, normal, or oligohydramnios. In no case was either antenatal surgical intervention or premature induction of labour undertaken. When a urinary tract anomaly had been detected antenatally, the patients all had serial sonographic examinations either antenatally or postnatally. The same paediatrician examined all the infants after birth. Repeat ultrasound examinations were done at 6 days and at 6 weeks after delivery or earlier in infants in whom moderate or severe dilatation of the calyces had been seen prenatally. Micturating cystourethrograms and intravenous urograms were performed in 15 cases to establish the diagnosis, and surgical evaluation and correction were undertaken in three.

Results

From 1 January to 31 December 1986 3228 infants were born. A total of 4070 fetal ultrasound examinations were performed before 28 weeks' gestation, and an additional 761 fetal examinations were done after 28 weeks' gestation for obstetric reasons. No renal tract abnormalities were identified in the fetal ultrasound examinations before 28 weeks' gestation, even in those fetuses in which later scans showed urinary tract abnormalities. In the 761 fetal examinations done after 28 weeks' gestation there were 62 fetuses (8%) in which unilateral or bilateral dilatation of the upper urinary tract was found. No fetuses had obstruction of the bladder neck on ultrasound examination. All the infants who had renal abnormalities on later evaluation were in the group in which the total length of the fetal renal collecting system was dilated to more than 15 mm before full term.

The antenatal ultrasonographic findings are compared with the postnatal diagnoses in table 1. The postnatal ultrasound scans at the end of 6 weeks of life were normal in 40 of the infants. A further five infants were lost to follow up. The three infants who had antenatal diagnoses of renal tract malformations in association with other major congenital abnormalities all died. One fetus was anephric on scanning and Potter's syndrome was confirmed at necropsy. One fetus with bilateral hydronephrosis had congenital heart disease confirmed at necropsy, and one with hydronephrosis had trisomy 13.

Fifteen infants had persisting renal tract dilatations on postnatal ultrasound examination at 6 weeks of age, and so micturating cystourethrograms and intravenous urograms were performed (table 2). In eight of the 15 the examinations were normal, though three of the eight had large extrarenal pelvises, which are considered to be a variant of normal.

In seven of the 15 infants renal tract abnormalities were confirmed. There were two infants with grade

Table 1 *Antenatal and postnatal ultrasonographic findings in 63 patients*

	Total No	*No of deaths*
Antenatal findings:		
Absent kidneys	1	
Dilatation of renal pelvis	62	
Postnatal findings:		
Potter's syndrome	1	1
Hydronephrosis and trisomy 13	1	1
Hydronephrosis and congenital heart disease	1	1
Ultrasonography normal by 6 weeks of age	40	0
Ultrasonography abnormal at 6 weeks of age	15	0
Lost to follow up	5	Not known

Table 2 *Results of micturating cystography and intravenous urography in 15 infants with dilatation of the renal pelvis persisting after 6 weeks of age*

Results	*No of infants*
No abnormality	8
Unilateral obstruction of pelviureteric junction corrected by pyeloplasty	3
Minor unilateral obstruction of pelvi ureteric junction under observation	2
Vesicoureteric reflux grade 2 or 3	2

2 or 3 vesicoureteric reflux who were given long term antibiotic treatment. Five infants had obstructions of the pelviureteric junctions, and Hines-Anderson pyeloplasties were performed in three with relief of the obstruction. Two with minor obstructions were still under observation at the time of writing and were on long term antibiotic treatment because of recurrent urinary tract infections. Thus 10 of the 63 fetuses that had renal tract anomalies identified by ultrasonography screening (16%) had pronounced renal tract abnormalities in the neonatal period, three of which were associated with other lethal congenital malformations. We were able to identify seven fetuses with minor dilatation of the renal pelvises who had pronounced renal tract abnormalities that required postnatal treatment and that could not be diagnosed by clinical postnatal examination. This is an incidence of 9·2/1000 (seven of 761) fetuses scanned after 28 weeks' gestation.

Discussion

Early diagnosis of upper renal tract obstruction or reflux is unfortunately seldom possible from the clinical signs of a palpable abdominal mass, haematuria, or recurrent urinary tract infections, because these lesions are often symptomless until severe renal damage has occurred. The timing of the surgical correction is thought to be important in reducing chronic renal insufficiency, as the best results are achieved in infants operated on in the first year of life.[11]

We have analysed the efficacy of routine ultrasound screening for diagnosing fetal upper urinary tract dilatation after 28 weeks' gestation as part of the maternal antenatal evaluations. In the antenatal period we identified important renal tract abnormalities that could not be found by clinical examination of the newborn infant with a frequency of 9·2/1000 births. We also identified the infants with lethal congenital abnormalities in addition to renal abnormalities, who comprised 30% of the group. This is similar to the findings of Hobbins *et al.*[12]

In the early reports of the antenatal diagnosis of urinary tract abnormalities there was a marked bias towards severe cases[5 6 12] and only a few cases were found to be normal in the postnatal period. Nicolini *et al*[13] however, reported a frequency of false positives of 43%. Their series included a number of cases referred because of suspicious ultrasound findings. In our study of patients from the obstetric population of one hospital, the rate of disappearance of dilatation of the renal pelvis during antenatal or postnatal life was much higher (83%). We have, however, followed up a group of fetuses identified mainly by minor degrees of dilatation of the renal pelvis.

Arger *et al*[10] reported that any fetus with a renal pelvis larger than 10 mm had pronounced hydronephrosis warranting close follow up. A morphologic classification of fetal urinary tract dilatation has been proposed by Grignon *et al*[8] who suggested that an anterior posterior diameter of the renal pelvis of less than 10 mm should be considered physiological as this disappeared in 97% of the infants in their study. Our study confirms these findings. We found that an abnormality was likely in those fetuses with dilated renal infundibula, or visible calyces, or both. The total length of the collecting system was greater than 15 mm before full term in all the infants who had renal abnormalities on follow up examination.

We found, however, that in several cases the degree of dilatation in the fetal period did not correlate with the chance of serious abnormality requiring surgical correction later. In some cases minor dilatation of the fetal renal pelvis progressed to severe obstruction requiring postnatal surgical correction, while in others serious dilatation resolved completely during the period of observation, either in utero or after birth. This is in agreement with the findings of others.[9 13] Frequent antenatal and early and repeated postnatal ultrasonographic evaluations are therefore necessary.

The natural history of dilatation of the fetal renal pelvis is not yet completely understood. Fetal hydronephrosis without dilatation of the bladder seems to occur mainly after 28 weeks' gestation, as it was not diagnosed in any fetal examination before 28 weeks' gestation in our series. This may be due to a considerable increase in fetal production of urine from 27–32 weeks' gestation with correspondingly less increase in kidney size.[13 14]

The incidence of upper urinary tract abnormalities requiring postnatal treatment was higher in our series than in earlier reports[13 15] and this may be because we followed up all those with even minor degrees of fetal dilatation of the renal pelvis. The most frequent cause of hydronephrosis was obstruction of the pelviureteric junction, and surgical correction was required in some of the infants in the first few months of life resulting in satisfactory renal function. Other infants with minor delay at the pelviureteric junction continue to be evaluated and long term antibiotic treatment for recurrent urinary tract infections is required.

Nicolini *et al*[13] reported that mortality, morbidity, and renal damage were not associated with the time between prenatal diagnosis of hydronephrosis (when the bladder is normal) and operation (when this is performed in the neonatal period). They agreed with Berkowitz *et al*[16] who did not recommend premature induction of labour or shunt placement in utero with its attendant risks. Antenatal operation should be considered only for severe bilateral obstruction of the upper urinary tracts—which is extremely rare—or for severe dilatation of a solitary kidney. Bilateral dysplastic kidneys follow complete obstruction early in development, and the fetus with this abnormality has a poor prognosis.[16] The development of oligohydramnios seemed to be the most reliable indication of severe impairment.[17]

There are different degrees of severity of vesicoureteric reflux, and infants with gross reflux under the age of 1 year are those most at risk of developing renal parenchymal damage.[18] Primary vesicoureteric reflux is an autosomal dominant congenital lesion with variable clinical expression,[19] and early detection would permit early antimicrobial prophylaxis or corrective operation, or both. It is possible that routine renal ultrasonography after 28 weeks' gestation would detect some of the fetuses with severe vesicoureteric reflux, we found two in whom early treatment was possible.

Reflex nephropathy can have serious complications—such as hypertension—and was the principal diagnosis in 12% of the patients entering one dialysis and transplant programme.[20] The capability of a general ultrasound screening programme to detect fetal urinary tract malformation has also been evaluated by Helin and Persson.[15] They performed routine ultrasound examinations at 17 and 33 weeks' gestation, and almost all the renal abnormalities were found at the second examination. Our study confirms these results, and we suggest that all pregnant women should have a second routine ultrasound examination performed after 28 weeks' gestation to identify fetal malformations in the renal tract as well as growth and obstetric abnormalities.

This approach should be investigated further to delineate the natural progression of fetal renal tract abnormalities and to calculate the cost effectiveness of fetal screening in reducing late complications by early evaluation and treatment of asymptomatic neonates.[19 21]

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Biotinidase deficiency: a survey of 10 cases

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SUMMARY Ten patients with biotinidase deficiency were studied. Clinical findings at presentation varied with dermatological signs (dermatitis and alopecia), neurological abnormalities (fits, hypotonia and ataxia), and recurrent infections being the most common features, although none of these occurred in every case. Biochemically the disease is characterised by metabolic acidosis and organic aciduria. Treatment with biotin results in pronounced, rapid, clinical and biochemical improvement, but some patients have residual neurological damage comprising neurosensory hearing loss, visual pathway defects, ataxia, and mental retardation. The cause of this permanent damage remains obscure and it is not clear if the early introduction of treatment will prevent it.

Biotin is a cofactor required by acetyl CoA carboxylase (ACC) [EC 6.4.1.2], pyruvate carboxylase (PC) [EC 6.4.1.1], propionyl CoA carboxylase (PCC) [EC 6.4.1.3] and 3 methyl crotonyl CoA carboxylase (MCC) [EC 6.4.1.4].[1] It is covalently attached to the apocarboxylases by the epsilon amino group of a lysine residue, where it functions at the active site as a carbon dioxide carrier in the carboxylation reactions. Biotinylation of the apocarboxylases is catalysed by holocarboxylase synthetase in an adenosine triphosphate dependent reaction with the intermediate formation of biotinyl adenosine monophosphate.[2] The turnover of carboxylases yields biotinyllysine (biocytin) from which biotin is regenerated by the action of a specific amidolyase, biotinidase [EC 3.5.1.12]. This enzyme is also required for the release of dietary protein bound biotin.

Individual inherited disorders of all four biotin dependent carboxylases have been reported.[3-9] In addition, patients with simultaneous defects of all four enzymes (combined carboxylase deficiency) who showed remarkable clinical and biochemical responses to pharmacological doses of biotin have been described. In some patients (usually neonates) this biotin responsiveness is also expressed in cultured cells whereas in others (who usually present later) no defect can be found. In the majority of patients with late onset combined carboxylase deficiency the underlying defect is biotinidase deficiency.[10] The early onset form, on the other hand, is due to holocarboxylase synthetase deficiency.[11] Thus combined carboxylase deficiency can be caused by either a functional biotin deficiency (biotinidase deficiency) caused by failure to recycle endogenous biotin and to liberate dietary biotin, or by defective biotinylation of apocarboxylase because of a mutant holocarboxylase synthetase that has an increased K_m with respect to biotin.[12] In both these inborn errors, treatment with pharmacological doses of biotin may correct the disorder.

Holocarboxylase deficiency usually presents acutely in the neonatal period but occasionally becomes apparent later. It is characterised by severe metabolic acidosis, organic aciduria, hyperammonaemia, lethargy, hypotonia, and vomiting. Biotinidase deficiency shows a less consistent clinical picture and Wolf *et al*[13] documented the phenotypic variations though some of the cases were misassigned.[14] The occurrence of persistent auditory and visual defects is now well recognised.[13 15 16]

We present our findings in 10 cases of definite biotinidase deficiency and suggest that although there is complete resolution of the biochemical abnormalities, there may be residual defects in some patients.

Case reports

Symptoms at presentation and long term complications are summarised in the table.

CASE 1

This patient was first described by Bartlett *et al* (case 3).[17] She was born in 1974 weighing 3350 g, the first child of related Irish parents; she has a younger

Table *Clinical presentation and outcome of 10 cases of biotinidase deficiency*

	Case No									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8**	*9*	*10*
Age at onset (months)	5	10	3	2·5	7	1·5	8	*	18	18
Age treatment started (months)	10	15	22	8	7·5	17	9·5	2·5	24	24
Symptoms:										
Ataxia	No	Yes	Yes	No	No	Yes	Yes	*	Yes	Yes
Hypotonia	Yes	Yes	Yes	No	No	Yes	Yes	*	Yes	Yes
Fits	No	No	Yes	Yes	Yes	No	Yes	*	No	No
Developmental delay	No	No	No	Yes	No	Yes	No	*	No	No
Alopecia	Yes	Yes	Yes	Yes	No	Yes	Yes†	*	No	Yes
Dermatitis	No	Yes	No	Yes	No	Yes	No	*	No	Yes
Respiratory infections	Yes	Yes	Yes	Yes	No	Yes	Yes	*	Yes	No
Long term complications										
Auditory	Yes†	Yes†	Yes†	No	No	No	Yes†	No	Yes†	No
Visual	No	Yes†	Yes	No	No	No	No	No	No	Yes
Intellectual	No	No	Yes	No	No	Yes	No	No	No	No
Ataxia	No	No	No	No	No	No	Yes	Yes†	Yes	No

*Receiving presymptomatic treatment †symptoms diagnosed or presenting during treatment

sister who is well. She developed normally until she was 5 months old when, after an upper respiratory tract infection, she was noted to be hyperventilating. This persisted and at the age of 8 months she was admitted to hospital for investigation. During the next two months she became so hypotonic that virtually all spontaneous movement ceased. She had a persistent compensated metabolic acidosis, and urinary organic acid analysis at the age of 10 months showed large amounts of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine. Based on these findings a diagnosis of MCC deficiency was made and treatment with biotin (5 mg twice a day, later reduced to 5 mg daily) was started. Within 24 hours the hyperventilation stopped, and by the end of a week there had been considerable improvement in the hypotonia. When reviewed at the age of 11½ months she was alert, could sit unsupported, reach out, and play.

At the age of 20 months she was thought to be normal, but at the age of 2½ years her speech was delayed and she had a profound neurosensory hearing loss. Apart from juvenile glaucoma diagnosed at the age of 6, development has otherwise been normal. Studies on cultured skin fibroblasts brought the diagnosis of MCC deficiency into doubt as the activities of two of the carboxylases were normal (R Chalmers, personal communication). Biotinidase activity was later undetectable.

CASE 2

This patient has already been described by Taitz *et al*, Charles *et al*, and Taitz *et al* (case 1 in each report).[16 18 19] He was born in 1977 weighing 2900 g, the second child of unrelated English parents; his older sister is normal. Although he suffered from recurrent respiratory tract and eye infections he progressed normally until the age of 10 months when he developed a rash and alopecia, and became unsteady with truncal ataxia. Acid base balance at that time was normal.

By the age of 15 months he had regressed to a developmental age of 1 month and was profoundly hypotonic. At this time a metabolic acidosis was noted; plasma lactate was raised (8·9 mmol/l, normal range 0·56–2·2 mmol/l) and urinary organic acid analysis showed excessive amounts of 3-hydroxyisovalerate, 3-methylcrotonylglycine, methylcitrate, and 3-hydroxypropionate.

He was given biotin 10 mg a day with remarkable effect. His neurological state returned to normal within three days, the dermatosis, alopecia, and recurrent eye infections resolved, and the respiratory infections improved. He now has a neurosensory hearing loss as well as a conductive hearing loss secondary to glue ear, and profound myopia with evidence of acquired retinal dysplasia. These defects were not detected before the biotin was started and they now seem to be stable as he has had no further deterioration in his visual or hearing acuity for four years. Development otherwise has been normal and at the age of 9 years he was making good progress intellectually, was in the upper stream in his class, and was thought to be well above average in his academic ability. Biotinidase was measured later; no activity was detected.

CASE 3

This patient was first described by Taitz *et al* (case 3).[16] He was born in 1979 weighing 2020 g, the second child of unrelated Indian parents. Apart from being 'chesty' he was well until the age of 3 months when he developed convulsions that were not controlled by phenobarbitone. Acidosis was not noted. Development was normal during the first year but thereafter he began to regress. At 16 months he became unwell with a pyrexial illness, diarrhoea, vomiting, and a chest infection; he also developed alopecia. There was no note of acidosis.

At the age of 22 months he was admitted to hospital for investigation where he was found to be hypotonic and grossly ataxic, and had regressed to a developmental age of 11–12 months; he was bald and tachypnoeic with a chronic chest infection. Fundoscopy showed no abnormality, but visual evoked responses suggested the possibility of some loss of function of the visual pathways or cortex. Urinary organic acid analysis showed a large excess of 3-hydroxybutyrate and 3-hydroxyisovalerate. Leucocyte carboxylase activities were reduced (PCC 3·0%, MCC 0·8%, PC 0·8%, and ACC 2·3%, expressed as percentages of the means of the normal ranges). Biotin 10 mg a day was started and resulted in neurological improvement within days, his hair regrew, and the chest infections occurred less often. Leucocyte carboxylase activities returned to normal. His speech, however, did not progress and he was found to have a severe neurosensory deafness. His development is also generally mildly delayed. Biotinidase activity was subsequently undetectable.

CASE 4

This boy was born in 1979 weighing 1480 g, the second child of related parents of Scottish tinker stock. An older sister is well and another child was stillborn at 34 weeks' gestation. He is related to two other children with biotinidase deficiency (case 6 in the present report and case 2 reported by Taitz *et al*[16]). He was delivered at 37 weeks' gestation by caesarean section for fetal distress preceded by intrauterine growth retardation. At 10 weeks he had a generalised convulsion that was treated with phenobarbitone. At the age of 3 months he had three more fits and the dose of phenobarbitone was increased. He was admitted to hospital at the age 5 months for repair of a strangulated hernia at which time it was noted that he was failing to thrive, and it was found that he had a history of recurrent upper respiratory tract infections, blepharitis, and staphlococcal skin infections. Alopecia, developmental delay, and regression were also noted and an intermittent compensated metabolic acidosis was found. At the age of 6 months the fits recurred and despite treatment with anticonvulsant drugs progressed to status epilepticus. The mild metabolic acidosis persisted with a raised plasma lactate concentration (4·8 mmol/l, normal range 0·67–1·7 mmol/l). Urinary organic acid concentrations were normal. By the age of 7 months there was a constant profound metabolic acidosis and analysis of urinary organic acids revealed excessive excretion of 3-hydroxyisovalerate and 3-methylcrotonylglycine. Leucocyte carboxylase activities were reduced (PCC, PC, and MCC all less than 1% of normal). Plasma biotin concentration was 0·3 mmol/l (normal 0·29–1·9) measured by an avidin binding assay that does not distinguish between biotin and biocytin.[17]

At the age of 8 months biotin 10 mg a day was started and within four days it was possible to stop all anticonvulsant treatment. Leucocyte carboxylase activities returned to normal (PCC 63%, MCC 113%, and PCC 61%, all activities expressed as percentage of the means of normal ranges) and the plasma biotin concentration was 113 mmol/l.

At the age of 5½ years he appeared to be developing normally within his cultural and social background. Hearing and vision seemed normal, although formal testing was not done.

CASE 5

This girl was born in 1982 weighing 2730 g, the third child of related Pakistani parents. One sibling died at the age of 4½ months of 'twitching', the other, 4 years older than the patient, was well at the time of writing.

She was admitted to hospital at the age of 7 months with tachypnoea of sudden onset and twitching of the face and limbs. She was found to be developmentally normal although unable to sit unsupported; tone and reflexes were normal. She had a persistent compensated metabolic acidosis (hydrogen ion concentration 39 nmol/l, base deficit −10 mmol/l) and plasma concentrations of pyruvate and lactate were raised (0·12 mmol/l, normal range 0·041–0·067, and 2·98 mmol/l, normal range 1–1·8, respectively). The twitching ceased when the acidosis was corrected with bicarbonate. Five days later the twitching recurred and she became hypotonic with poor head control. A metabolic acidosis was noted (hydrogen ion concentration 40 nmol/l, base deficit −7·3 mmol/l). Urinary organic acids were abnormal with a large excess of 3-hydroxyisovalerate, and concentrations of 3-methylcrotonylglycine, methylcitrate, and 3-hydroxypropionate. A provisional diagnosis of 3-methylcrotonylglycinuria was made and she was given biotin 5 mg twice a day. She improved within four days, and three weeks later was able to sit unsupported. Since that time she has remained well with no evidence of developmental delay, or visual or auditory problems. Biotinidase deficiency was later proved.

CASE 6

This girl was born in 1981 weighing 2810 g, the first child of related Scottish tinkers and is related to case 4 in the present study and to another child with biotinidase deficiency (case 2 reported by Taitz *et al*[16]). She had recurrent stridor from the age of 6 weeks resulting in several admissions to hospital and at 16 months she was admitted acutely ill with a 24 hour history of fever, vomiting, stridor, and drowsiness; she was hypotonic and comatose with truncal ataxia, stridor, alopecia, and a rash. Her condition improved after intravenous fluid replacement but she had gross developmental delay (a developmental age of 5 months) and small head circumference for her age. She had a metabolic acidosis and raised plasma lactate and pyruvate concentrations (3·3 mmol/l, and 0·12 mmol/l, respectively); analysis of her urine showed excessive excretion of 3-hydroxyisovalerate, 3-hydroxybutyrate, succinate, and 3-hydroxy-3-methylglutarate. Plasma biotinidase activity was undetectable.

She was given biotin 5 mg twice a day, and improved within three weeks, further improvement was steady with no recurrence of the respiratory or cutaneous features. Head growth has since been satisfactory but there is some cognitive delay (developmental quotient 38 months at 46 months). There was no evidence of visual problems or of auditory handicap (clinically, with brain stem evoked responses, or on audiometry) either before or after treatment.

CASE 7

This boy was born in 1982 weighing 3160 g, the first child of unrelated British parents. He was initially well with normal development and could sit unaided at the age of 7 months, but at the age of 8 months he presented with ataxia, hypotonia, seizures, and recurrent respiratory infections. Investigations showed a persistent metabolic acidosis with raised plasma lactate concentration (maximum 4·75 mmol/l) and urinary organic acid analysis showed increased 3-hydroxyisovalerate and 3-methylcrotonylglycine. Plasma biotinidase activity was unrecordable Biotin 10 mg a day resulted in considerable improvement within 24 hours and this continued until all his symptoms resolved apart from a mild limb and truncal ataxia. Alopecia developed immediately after the start of treatment but subsequently resolved. Neurosensory deafness was noted later (this had not been tested before treatment).

Development, apart from some speech delay (probably secondary to deafness), has been within normal limits. Mild limb and truncal ataxia continued to be present at 4½ years of age and intermittently became more severe, usually in association with minor infections. These exacerbations are resolved by temporarily increasing the biotin dose to 15 mg daily, but compliance may not be good.

CASE 8

This patient has previously been described by Wallace.[20] He was born in 1984 weighing 3500 g, and is the full brother of case 7 in this report, the second child of the parents. Biotinidase deficiency was diagnosed presymptomatically in a sample of cord blood and confirmed in a sample of venous blood at 4 weeks of age. Biotin 10 mg daily was started at the age of 10½ weeks. Hearing and vision seemed to be unaffected before treatment. He developed normally with no symptoms of typical biotinidase deficiency, but when he was 2½ years old he was noted to have a mild ataxia though continuing on treatment; compliance, however, may not have been good. At 3½ years of age his hearing, vision, and coordination are normal.

CASE 9

This boy was born in 1983 weighing 4120 g, the first child of unrelated English parents. He developed normally during the first year although he was always thought to be excessively clumsy. From about 18 months old he became increasingly unsteady and developed frequent upper respiratory tract and chest infections At the age of 22 months he was hyperventilating, hypotonic, and grossly ataxic in gait and speech; vision and hearing seemed normal. His hair and skin were normal but there was mild erythema of the conjunctivae. He had a compensated metabolic acidosis with a normal lactate concentration (1·9 mmol/l—reference range 0·6 to 2·4) and raised pyruvate concentration (0·18 mmol/l—reference range 0·04 to 0·08) Urinary organic acid excretion was abnormal with excessive amounts of 3-methylcrotonate, 3-hydroxyisovalerate and 3-methylcrotonylglycine. Leucocyte carboxylases were decreased (PCC 17%, MCC 17%, PC <1%, all activities expressed as percentages of the means of the normal ranges).

Biotin 10 mg a day was started and his neurological state improved within four days; this continued for several weeks, eventually all the signs completely resolved. After about two months the dose of biotin was reduced to 1 mg a day He remained on this regimen for three months when, during a febrile illness, he became mildly ataxic again and the dose of biotin was returned to 10 mg a day. Since then he has remained well and has developed normally but he tends to become ataxic during intercurrent illnesses and his fine movements are rather clumsy At the age of 3½ years his hearing was normal, but at 4 years 3 months he was found to be deaf with a neurosensory hearing loss.

CASE 10

This girl was born in 1983, the third child of related Iranian parents. Their first child had died at the age of 1½ years of pneumonia and skin lesions, and the second child had died at the age of 1 year of gastroenteritis. Their fourth child seems to be normal.

The patient was well until the age of 1½ years when she developed an extensive erythematous rash and alopecia. A tentative diagnosis of acrodermatitis enteropathica was made and zinc supplements were given. Shortly afterwards she developed gastroenteritis, a metabolic acidosis, and exacerbation of her rash. This improved and she was discharged from hospital taking zinc supplements. The rash resolved but recurred at 2 years of age when she again developed a severe metabolic acidosis, fever, signs of cerebellar ataxia, myoclonic jerks, and exaggerated tendon reflexes. Urinary amino acid analysis showed raised concentrations of branched chain amino acids and a diagnosis of intermittent maple syrup urine disease was made. She was discharged on a low protein diet with supplements of Milupa MSUD2; the neurological signs resolved within a month and the rash and alopecia within two months. For the next 18 months she continued on a low protein diet. The rash recurred repeatedly, improving when she was given two scoops of Milupa MSUD2 formula only to reappear after about 12 days. Her development was otherwise normal.

At the age of 3½ years she was referred from Iran to the United Kingdom where she was found to have mild dermatitis around the nares and was generally hypotonic with brisk tendon reflexes. She had optic atrophy but good visual acuity, and hearing was normal. A clinical diagnosis of biotinidase deficiency was made and confirmed by enzyme assay. Biotin 5 mg twice a week resulted in complete resolution of the rash within four days and return of muscle tone to normal. (Milupa MSUD2 contains 0·3 mg of free biotin/100 g and two scoops of formula provides about 30 μg of free biotin.)

Discussion

From the cases described here and from other reports it seems that the presentation of biotinidase deficiency may vary. The onset may be acute or insidious, with either a steady progression or a series of acute incidents interspersed with periods of apparent normality. Hypotonia, ataxia, fits, dermatitis, alopecia, and recurrent respiratory infections are the most common clinical features, but none of these is seen in all cases. Even the metabolic acidosis may not be a constant feature, and urinary organic acid excretion may be unremarkable particularly early in the disease.

Although the immediate response to biotin may be considerable, with complete resolution of the metabolic, skin and, hair abnormalities, it is becoming increasingly obvious that there may be long term complications. Neurosensory deafness and impairment of the optic nerve and visual pathways are now well recognised, and have been described in this report (cases 1, 2, 3, and 7, and cases 1, 2, 3, and 10, respectively). The courses of the patients described here also suggest that intellectual impairment (cases 3 and 6) and persistent ataxia (cases 7, 8, and 9) may be encountered. The cause of these deficits is not clear, nor is it apparent whether the underlying damage occurs before the start of treatment, though it may not be recognised until later. It is important, however, to note that in one case (case 8) ataxia developed despite presymptomatic treatment with biotin, and that in case 9 neurosensory deafness, which had been shown to be absent initially, developed while the child was receiving regular treatment.

Though this does not preclude the possibility that the underlying damage occurs earlier, it may indicate that the damage continues after treatment has been started and it seems that a more guarded prognosis is necessary even when the child seems normal at the time of diagnosis. Neurological damage may be the result of high concentrations of biocytin in conjunction with low concentrations of biotin and the biotin dose should therefore be kept to a minimum to lower the rate of turnover of carboxylases and thus the rate of production of biocytin or biotinyl peptides or both. It is of interest that in a few cases low doses of biotin seemed enough to control the metabolic abnormalities, though the other manifestations may not resolve entirely unless higher doses are given (case 10). Other patients require much larger doses and requirements are increased by intercurrent mild illnesses (cases 7 and 9).

In view of the variation in the clinical presentation and of the occurrence of long term complications and the apparent differences in biotin requirements, the possibility that biotinidase may have an additional role (possibly as a biotin transport protein) should be considered. It could then be postulated that different symptoms could be assigned to the deficiency of different functions and that in some cases only one function is lost. The fact that the occurrence of persistent deficits varies within a kinship, however (cases 4 and 6 had no long term visual problems though the related child, case 2 described by Taitz *et al*,[16] developed optic atrophy), seems to disprove this hypothesis.

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Adenovirus infection in families

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SUMMARY Eighteen families were followed up for four to six weeks after one member of each family was diagnosed as having an adenovirus infection. In 17 of 18 index cases the diagnosis was based on the rapid detection of adenovirus hexon antigen in the nasopharyngeal mucus specimens and in one case (the only adult index case) on isolation of the virus. All index cases had high temperatures associated most commonly with tonsillitis, acute otitis media, gastroenteritis, or febrile convulsions. In 14 of the 15 families with symptomatic contacts the index case was the first symptomatic case, or one of the first symptomatic cases, in that family. Fifteen (94%) of the siblings and 20 (56%) of the parents had signs and symptoms of acute infection during the follow up period. In 10 (63%) and eight (20%) of these cases, respectively, adenovirus was confirmed. The mean (SD) incubation period of confirmed adenovirus infections was 10 (3) days. The observations show that adenovirus infection spreads actively to other siblings in the family. Rapid diagnosis permits parents to be informed prospectively about the expected spread and clinical picture of the illness in the family

Adenoviruses are a common cause of febrile infections in children. Because the infection often lasts a long time and may be difficult to distinguish from bacterial infection, rapid diagnosis is important.[1-4] Detection of adenovirus hexon antigen with immunoassay has been developed in our laboratory by Halonen *et al*[5 6] and used in routine diagnostic work since 1981. During these seven years the clinical value of this test has been proved[4 7 8] and about 700 cases of adenovirus illness have been diagnosed. We report that rapid diagnosis of a primary case in a family is clinically important, because the infection spreads actively to siblings.

Patients and methods

The study was carried out between September 1984 and February 1985. During that period 974 specimens of nasopharyngeal mucus were taken for rapid virus diagnosis (NPS test) from febrile children at Turku University Hospital (622 samples) and at a private paediatric clinic (352 samples). Adenovirus antigen was isolated from 55 samples and the information was available to investigators 24–48 hours after the sample of mucus had been taken. Twenty families were contacted within five days of diagnosis of the index case. Three families refused to enter the study and 17 gave informed consent. In addition, the NPS test was negative in one adult index case (house officer of the department of paediatrics) but the virus was isolated. Eleven index cases were diagnosed at Turku University Hospital and seven in a private paediatric clinic.

Follow up questionnaires were given to parents, and samples of blood were taken for viral studies. After four to six weeks, follow up questionnaires were returned and samples of blood were again taken for serological tests. Forty six paired serum samples and seven single serum samples were obtained from 53 contacts. Specimens for the NPS test and for virus isolation during the follow up period were collected from 40 and 22 of the contacts, respectively. Haematological tests were done using routine techniques.

EZYME IMMUNOASSAY (ELISA) FOR ADENOVIRUS ANTIGEN

Nasopharyngeal specimens were collected by suction through the nostrils with a disposable mucus extractor (Vygon, Ecouen, France) and diluted 1:5 in phosphate buffered saline. The indirect ELISA used to detect adenovirus antigen has previously been described in detail.[6] The assay detects a true infection in children.[7] The specimens were tested in parallel for respiratory syncytial virus, influenza A and B virus, and parainfluenza virus types 1, 2, and 3 antigens by analogous assays.

ELISA FOR ADENOVIRUS ANTIBODY

The ELISA for IgG and IgM antibodies to adenovirus hexon antigen has previously been described[7] A fourfold or greater increase in the concentration of IgG in paired serum samples, or the detection of IgM antibodies, indicated a recent infection.

VIRUS ISOLATION

Adenovirus isolation from throat swabs were carried out in HeLa cells using routine laboratory methods.

Results

At the time of the diagnosis of adenovirus disease 10 of 18 index cases were the only symptomatic cases in the family—that is, primary cases. In four cases the symptoms of the index case began at the same time as those of other family members. In two cases febrile infection had already occurred in other family members, in both cases in parents. In two cases insufficient information was obtained concerning the family history at the time of the diagnosis of the index case. Serological tests from paired serum samples were carried out from 14 of 17 index patients in whom the NPS test was positive, and these indicated recent infection in 13 cases. The one index patient in whom the NPS test was negative but from whom the virus was isolated also had a considerable increase in IgG antibodies to adenovirus.

Tables 1 and 2 shows the main characteristics of the 18 index cases. With one exception, all were children with a mean age of 2·2 years. There were 10 girls and eight boys. All index cases had high fevers, and the most common signs and symptoms were tonsillitis, otitis media, febrile convulsions, and gastroenteritis.

During the four to six week follow up period, symptoms and signs of acute respiratory infection were recorded in non-index family members of 16 of the 18 families studied (table 3) With one exception, all other 16 siblings in the study families developed symptoms. Evidence of adenovirus infection was found in 10 of 17 siblings; in four the NPS test was positive (serological response was studied in three of them and was positive in all) and in six the NPS test was negative, but they had considerable seroresponses, one of them having the virus isolated from serum. One sibling had a parainfluenza type 1 infection (by the NPS test) that began 20 days after the onset of the adenovirus infection in the index case. Twenty (56%) of the parents became symptomatic. All 23 NPS tests from parent contacts were negative as were all virus isolation studies Serological evidence of adenovirus infection was obtained in four cases. In addition, four parents showed considerable increases in adenovirus IgG antibody titres, but were asymptomatic. Two symptomatic parents had high adenovirus IgG antibody titres but no significant increase was found. In six cases the timing of taking the blood samples for serology was not optimal for detection of the virus because the first sample was taken too late after the onset of symptoms. The mean (SD) incubation period calculated from the first symptomatic day of the primary case (calculated reliably in 17 cases) was 13 (6) days for the whole group and 10 (3) days for serologically confirmed cases (n=9).

The clinical picture in contact siblings was characterised by high fever, rhinitis, and cough. Half the

Table 1 *Main characteristics of 18 index cases with adenoviral infection*

	Mean (range)
Age (years)*	2·2 (0·5–7·8)
Duration of fever of the time of diagnosis (days)	3·3 (0–10)
Highest temperature (°C)	39·6 (38·2–40·7)
Erythrocyte sedimentation rate (mm in the first hour) (n=5)	62 (16–85)
C reactive protein (mg/l) (n=12)	49 (0–180)
White cell count $\times 10^9$/l (n=11)	15·8 (5·4–23·9)

*One adult (aged 32 years) excluded

Table 2 *Diagnoses**

	No
Tonsillitis	7
Otitis media	6
Febrile convulsion	3
Gastroenteritis	3
Fever without focus of infection	2
Upper respiratory tract infection	2
Conjunctivitis	1
Urticaria	1

*Some patients have more than one diagnosis

Table 3 *Symptoms of infection in family contacts of a patient with adenoviral disease*

	Siblings (n=16) *No (%)*	*Parents (n=36)* *No (%)*
Total signs and symptoms of infections	15† (94)	20† (56)
Fever ⩾37·5°C	10 (63)	8 (22)
Pain in swallowing	4 (25)	17 (47)
Hoarseness	1 (6)	10 (28)
Upper respiratory tract infection	11 (69)	16 (44)
Exanthema	2 (13)	3 (8)
Gastroenteritis	8 (50)	5 (14)
Conjunctivitis	3 (19)	3 (8)

*One sibling in whom the nasopharyngeal mucus test was positive for parainfluenza type 1 infection excluded, †adenovirus infection was confirmed in 10 siblings and in four parents patients had gastrointestinal symptoms (table 2). Three of the sibling contacts were treated with antibiotics, two because of otitis media, and one because of an upper respiratory tract infection with fever. In the parents the major symptoms were pain on swallowing, rhinitis, and cough. Additionally many of the adult contacts had symptoms of laryngitis—for example, hoarseness. Only one (3%) of the parents had temperatures exceeding 39·0°C whereas the corresponding number in siblings was seven (41%). Vomiting, diarrhoea, and abdominal pains were more common among siblings than among parents. Four parents were treated with antibiotics for upper respiratory tract infections.

Discussion

This study confirms our earlier experience that rapid diagnosis of adenovirus infection is of great clinical value.[7 8] Adenovirus often causes a more serious illness than other respiratory viruses.[5] In addition, adenovirus infections are commonly associated with a high white cell count ($>15\times10^9/l$), increased erythrocyte sedimentation rate (>30 mm in the first hour), and increased serum C reactive protein concentration (>40 mg/l). These also differentiate them from other respiratory virus infections and make the clinical management more difficult.[4 8 10]

The rapid diagnostic test we used is simple and inexpensive and can be carried out in any modern virus laboratory. Quick fluoroimmunoassay technology had recently been applied to the detection of the adenovirus antigen permitting the diagnosis in 30 minutes.[11 12] We are currently testing this assay in clinical practice. It has been clearly shown that the NPS test detects a true infection,[7] and our study confirms this. Its sensitivity compared with virus isolation, however, has not been systematically studied. During this study we found two patients in whom the NPS test was negative but from whom the virus was subsequently isolated. We also found 10 symptomatic patients in whom the NPS test was negative but who developed considerable serological responses. This can be explained in some patients from whom the mucus sample could not be aspirated within the first five days of the onset of illness, because this is the optimal time for the diagnosis.[7] The results of this study (and of our earlier studies) suggest that the NPS test should be used as a primary diagnostic test. If it is negative and diagnosis is still needed, virus isolation and IgG antibody assay should be done.

Adenovirus infection is highly contagious. Several outbreaks of adenovirus induced pharyngoconjuctival fever in hospitals,[13 14] schools,[15] and day nurseries[16] have been described. In the Seattle virus watch study a large number of contacts were monitored, and 32 to 100% of the susceptible contacts became infected.[1] Our observations confirm these studies. In this family study a total of 94% of the siblings and 56% of the parents had signs and symptoms of acute infection during the follow up period of 4 to 6 weeks. Adenovirus disease was confirmed in 63% and 20% of these cases, respectively. This finding is consistent with the observations of Sterner *et al*[17] who confirmed the infection serologically in only 38% of their family contacts, but adenovirus was isolated from 85% of the cases and all had symptoms of adenovirus infection.

To see if patients had any other virus infections we did NPS tests and attempted virus isolation for many symptomatic contacts, but found only parainfluenza virus type 1 in one sibling. In addition to adenoviruses, parainfluenza virus was the only other respiratory virus detected in the community during the first four months of the study when 16 of the 18 index cases were diagnosed. This supports the idea that in most of the symptomatic contacts the illness was caused by adenovirus. It is further supported by the fact that the incubation periods of the laboratory confirmed, and the clinically diagnosed, cases did not differ significantly.

The important clinical observation that we made was that in 88% of the families with symptomatic contacts the index case was the first symptomatic case, or one of the first symptomatic cases, in the family. Adenovirus usually results in so fulminant an infection that the first symptomatic child is taken to a physician.[4] The rapid detection of adenovirus hexon antigen in nasopharyngeal mucus permitted us to diagnose the illness usually within 24 hours. The practical implication of these observations is that by using rapid virus diagnosis parents can be informed prospectively about the expected spread and clinical picture of the illness in the family. This information is especially important in adenovirus infections because they may be difficult to distinguish from bacterial infections.[4 8] In this study 11 of the 18 index cases were treated with antibiotics, whereas only seven of 35 symptomatic family members (three siblings and four parents) were treated when it was known that one family member had an adenovirus infection.

In the children in this study adenoviruses most commonly caused febrile exudative tonsillitis, acute otitis media, and gastroenteritis. This confirms our previous study of 105 hospital patients.[4] In parents the major symptoms were pharyngitis, cough, and rhinitis; high fever (39·0°C), however, was recorded in only one adult. The degree of contagion and the fulminant clinical manifestations of adenoviral infection emphasise the need for rapid diagnosis. In the

Turku area the extensive use of rapid diagnostic procedures for viral infections during the last seven years has resulted in increased awareness and clinical recognition of the signs and symptoms of adenovirus infection. Consequently in the present study most of the index cases were first suspected clinically as adenovirus infections.

In conclusion, this study stresses the need for generalised use of rapid diagnostic methods of adenovirus infections; not only does it help families, but it will be useful in nursery and school epidemics, especially those of severe illness induced by adenovirus type 7.[18] Rapid virus diagnosis will permit studies of antiviral drugs[19] and should have a pronouced influence on the proper use of antibiotics.

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Short reports

Sudden death in incomplete Kawasaki's disease

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SUMMARY A boy of 12 years died suddenly of myocardial infarction, which was due to coronary artery aneurysm typical of Kawasaki's arteritis. Two years earlier he had an obscure illness, recognised retrospectively as incomplete Kawasaki's disease. We recommend routine echocardiography even if only one or two features of the syndrome are present.

Kawasaki's disease is typically a disease of young children and the diagnostic criteria have been clearly defined.[1] Most children present between the ages of 1 and 5 years and the disease is rare after 7 years.[2] The association with coronary artery aneurysms and sudden death is also well established.[3] Recently incomplete Kawasaki's disease with coronary artery involvement has been described in five young children aged between 4 months and 2½ years, one of whom died in intractable heart failure.[4] We describe a case of a child of 12 years who died suddenly of myocardial infarction due to thrombosis of an abnormal left coronary artery which showed the features of Kawasaki's disease. Two years before his death he had had an illness, which retrospectively may have been incomplete Kawasaki's disease.

Case report

This boy, who had previously been well, was admitted at the age of 10 years with a 10 day history of pain in the region of the left ear and throat, and fever. He had been treated with cotrimoxazole without effect. On examination he looked ill and pale, he was holding his head still, and had difficulty in opening his mouth. He was afebrile, and there was no obvious swelling in the neck. He had a few slightly enlarged lymph nodes in the groin. Initial investigation showed a neutrophil leucocytosis (total white count $23 \cdot 2 \times 10^9/l$, neutrophils 91%) with toxic changes, a thrombocytosis (platelets $753 \times 10^9/l$), and a raised erythrocyte sedimentation rate of 107 mm in the first hour. Biochemical investigations and examination of the cerebrospinal fluid gave normal results. A radiograph of the neck showed increased lucency of the left mastoid process; ultrasound examination of the neck was normal.

A diagnosis of osteomyelitis of the mastoid was made and he was treated with intravenous fusidic acid and erythromycin. Over the next seven days he had a moderate intermittent fever, which then settled. His erythrocyte sedimentation rate on the third day after admission was 118 mm in the first hour and thereafter slowly declined. His platelets peaked at $1206 \times 10^9/l$ on the fifth day but remained raised throughout his admission. All cultures, virological investigations, tests for antistreptolysin O titre, antinuclear factor, anti n-DNA, mitochondrial antibody, smooth muscle antibody, and parietal cell antibody gave negative results. He developed a hard tender mass at the insertion of the sternomastoid, which gradually declined. On the ninth day after admission it was noted by the parents and recorded by the nurses that the tops of his fingers were peeling. He remained rather pale and miserable throughout his stay in hospital.

He was followed up in outpatients for several months; a fibrotic mass at the sternomastoid insertion gradually resolved; he remained easily tired and prone to viral infections. On one occasion he described a single episode of acute muscular pain in the chest and shoulder, which had resolved with paracetamol. Thereafter he remained very well. He had a normal exercise tolerance, took part in all sport, and did not ever complain of chest discomfort. Twenty three months after the illness he had been out walking with a friend, felt tired and went to lie down. A little later he complained of chest discomfort, then suddenly turned over, clutched at his chest, and died almost immediately. Attempts at resuscitation by the ambulance team and in the accident and emergency department were of no avail.

PATHOLOGY FINDINGS

At postmortem examination the heart weighed 220 g and showed aneurysmal dilatation of the left stem and proximal left anterior descending artery (fig 1). The dilated segment measured 2·5 cm in diameter and contained old and recent thrombi. The distal left anterior descending artery showed complete obliteration of the lumen by firm greyish tissue The proximal portion of the right coronary artery showed similar luminal occlusion; the circumflex artery remained patent. Microscopically the left coronary artery in its distended portion showed a loss of normal smooth muscle and replacement by fibrous connective tissue. The distal left anterior descending artery (fig 2) showed luminal occlusion by cellular fibrous connective tissue, representing an organised thromus. Recanalisation had occurred as evidenced by vascular channels of various size.

There was extensive fibrosis of the media and only a few disrupted remnants of the internal elastic lamella were noted The lungs showed oedema and congestion in keeping with acute heart failure after myocardial infarction due to thrombosis of an abnormal left coronary artery.

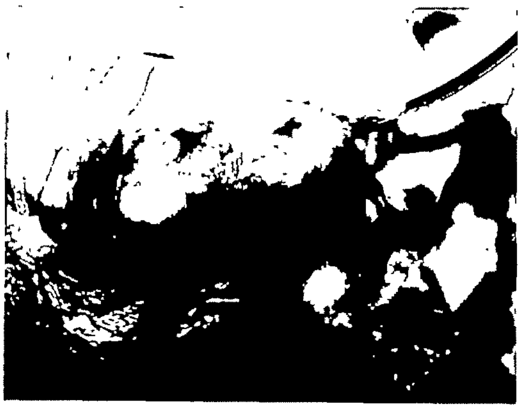

Fig 1 *A suture needle points to an aneurysm of the proximal left anterior descending artery*

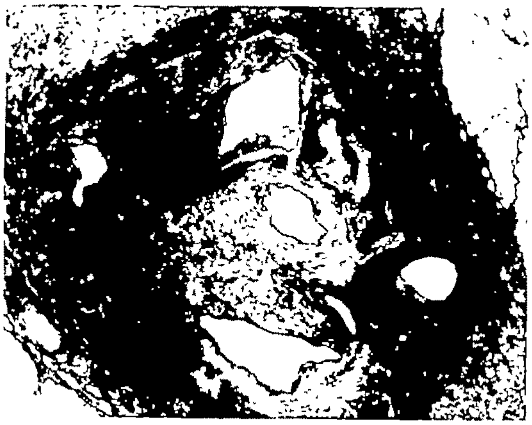

Fig 2 *The distal left anterior descending coronary artery shows evidence of old thrombosis and recanalisation. The internal elastic membrane is disrupted and frayed as a sequela of the initial vasculitis (elastic Van Gieson × 25).*

Discussion

Kawasaki's disease is a generalised vasculitis of unknown aetiology, which differs from the other vasculitic disorders by its propensity to effect the coronary arteries. The macroscopic and microscopic features of the coronary arteries in this case are typical of late stage Kawasaki's disease. This is well described by Hamashima as occurring between 40 days and four and a half years after the disease onset, and characterised by arterial scarring and recanalisation, in addition to the presence of aneurysms.[3]

In this case the acute attack occurred two years before the fatal thrombosis. A similar case of sudden death has been described in a 12 year old boy four years after the initial illness, with coronary artery pathology identical to this case.[5] This presentation was unusual in that there were no specific signs of Kawasaki's disease apart from finger desquamation. We conclude that this 'incomplete form' of Kawasaki's disease still carries the risk of coronary artery involvement.

There is now evidence that long term treatment with antiplatelet therapy may prevent secondary coronary thrombosis in adults.[6] The management of aneurysms of the coronary arteries in Kawasaki's disease is still controversial; currently low dose aspirin treatment is recommended for six months after the acute illness, but it may be appropriate to continue this treatment for much longer. Furthermore, coronary artery bypass surgery has been undertaken successfully in children with severe coronary artery abnormalities after Kawasaki's disease.[7]

We suggest that any child presenting with an illness associated with a raised platelet count and peeling of the fingers should have echocardiography to exclude lesions of the coronary arteries.

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A new chart for weight control in Duchenne muscular dystrophy

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SUMMARY Weight control is desirable in the muscle wasting conditions. A new chart is presented to allow the prediction of an ideal weight, free of excess fat, specifically for boys with Duchenne muscular dystrophy.

Patients suffering from muscular dystrophy often put on weight as the disease progresses It is not uncommon for boys with Duchenne muscular dystrophy to have weight values greater than the 90th centile on normal growth and development charts, despite having a smaller muscle mass than normal boys of the same age. It has been shown that therapeutic weight reduction is possible in these patients,[1] and loss of unnecessary fat lessens the burden of weakened muscles and aids mobility.

Prevention of excessive weight gain in the younger patient is preferable to severe dietary restriction in the already obese subject Normal growth and development charts make no allowance for the progressive loss of muscle that is occurring as the muscular dystrophy progresses throughout childhood. A child with pronounced muscle wasting looks 'cachectic' without the excess fat filling out his body contours, something parents find hard to accept. The loss of muscle coupled with reduced activity implies accumulation of fat tissue if weight gain approximates that of normal growth charts.

Method

The 24 hour excretion of creatinine in the urine as a breakdown product of phosphocreatine in muscle, assuming 1 mmol creatinine equals 2·2525 kg of muscle, provides a reliable estimate of the contribution of muscle to body weight in the absence of renal disease.[2]

Theoretical weight centiles for zero muscle mass can be drawn from data on normal creatinine excretion[1] and from standard weight and height centile charts.[3] From a knowledge of the patient's creatinine excretion the muscle bulk may be derived and added to the zero muscle weight chart to produce an ideal weight.

Results

A new chart is presented, which gives ideal weight guidelines for weight control in boys with Duchenne muscular dystrophy (figure). From observations of body composition and creatinine excretion in boys with Duchenne muscular dystrophy we have found a close relationship between the reduction in total body potassium and that of 24 hour urinary creatinine excretion.[4] Both total body potassium and urinary creatinine excretion, when related to the predicted values for the individual's height, declined with age at an average rate of 4% per year from 6 to 17 years.[4] A similar 4% per year loss in muscle strength has been observed in boys with Duchenne muscular dystrophy.[5] At 6 years a boy with Duchenne muscular dystrophy has only 60% of his predicted muscle mass, and at 16 years only 20%. The reduction in creatinine excretion can be calculated and from this the muscle bulk can be derived and added to the zero muscle weight charts. Based on this assumed 4% per year decline in muscle mass the 90th, 50th, and 10th 'ideal' weight centiles have been calculated to allow for progressive loss of muscle.

Discussion

This chart can be used in the normal way by selecting the appropriate height related centile. This chart is **only** applicable for Duchenne muscular dystrophy. In other muscle wasting conditions

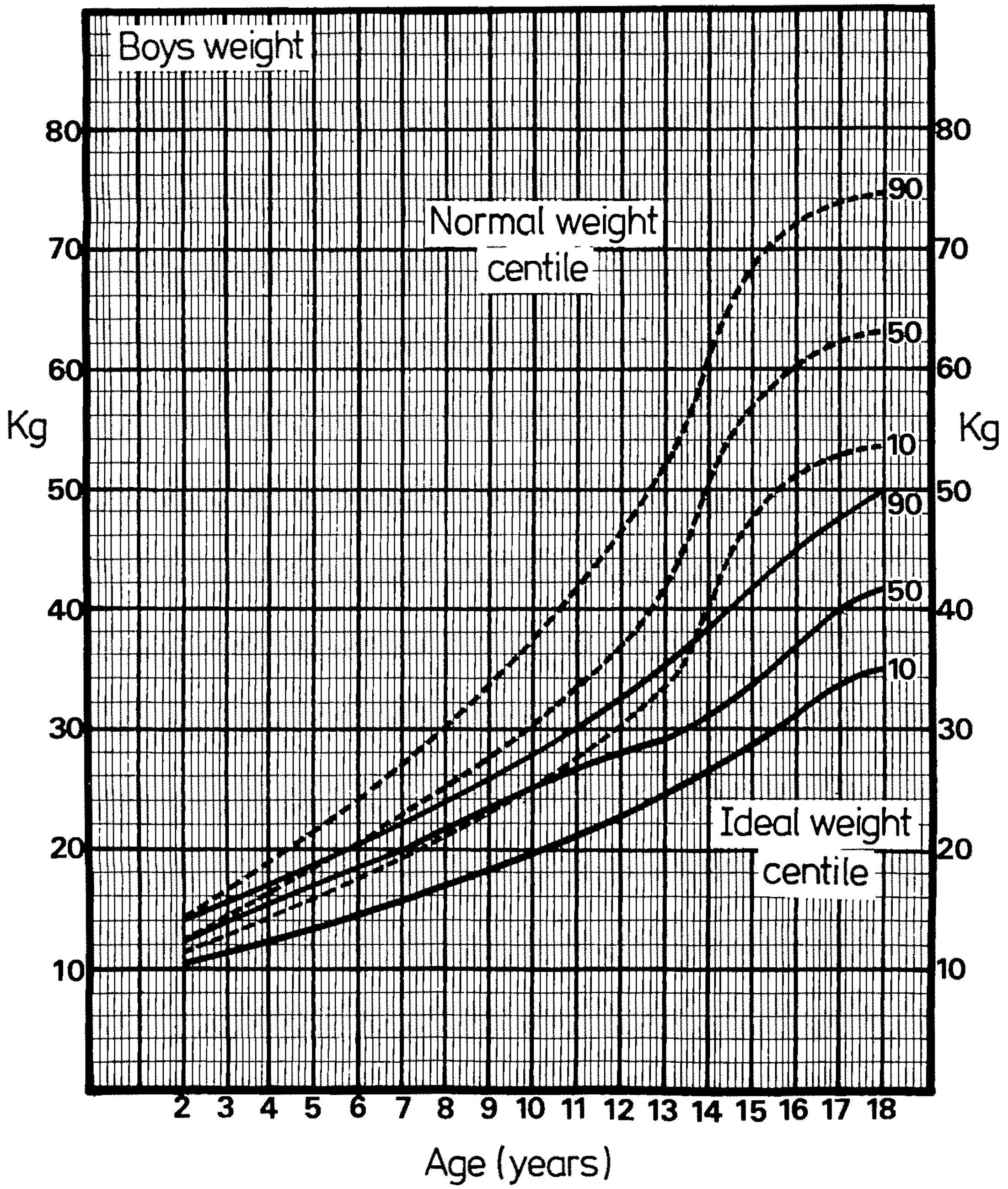

Figure *Ideal weight centile chart for boys with Duchenne muscular dystrophy. Based on data from Edwards et al,[1] Edmonds et al,[4] and Tanner and Whitehouse [3] Assumes a 4% per year decline in muscle bulk* measurement of 24 hour creatinine is advised with calculation of the ideal weight from the zero muscle chart.[1] To obtain a practical objective for dieting allowance must be made for the increased fibrous tissue accumulation that takes place in the dystrophic disease process.

How to use the chart

This chart is used in conjunction with the Tanner and Whitehouse longitudinal standards for height and weight.[3]

(1) Find appropriate height centile.

(2) Predicted 'ideal' weight is read off the chart using the height centile line.

(3) A practical objective for diet control is achieved by adding to the ideal weight an extra kg for every year the boy is over 10 years—for example, at 15 years this would be 5 kg extra.

The support of the Muscular Dystrophy Group of Great Britain and Northern Ireland is gratefully acknowledged

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See Annotation by Hulse on p. 1179.

Does ABO incompatibility matter?

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SUMMARY The incidence and severity (peak serum bilirubin concentration) of clinically detectable jaundice was determined retrospectively in 110 elution positive cases of ABO incompatibility. Neither the incidence nor the severity of jaundice in the study group differed significantly from a control group. In the individual case Coombs positivity and/or a strongly positive elution test may be a helpful predictor of jaundice occurring but not of its severity.

With the declining incidence of Rhesus disease, ABO incompatibility is said to be the commonest cause of haemolytic jaundice in the newborn. This is not surprising in view of the fact that 20–25% of pregnancies are ABO incompatible. Compared with Rhesus incompatibility, however, the jaundice is usually mild and characteristically later in onset. Furthermore, associated anaemia rarely occurs. These observations prompted us to consider the clinical importance of ABO incompatibility by a retrospective case-control study.

Patients and methods

In this hospital cord blood is routinely taken from the infants of all group O mothers. This is tested for blood group and presence of antibodies by an elution test and direct Coombs test. The elution test is performed by washing the infant's red cells twice in saline followed by heating to 56°C to dissociate the maternal antibody from the antigenic sites The resultant solution is centrifuged and the supernatant (eluate) tested against adult red blood cells of known group. Agglutination of the cells confirms the presence of specific antibody. The elution test detects maternal anti-A or anti-B haemolysins (IgG antibodies) on the infant's red blood cells.[1]

Routine screening was instituted in 1978 after reports that it reduced the need for exchange transfusions in ABO incompatible infants by allowing early detection.[2] Data were collected on 110 ABO incompatible deliveries (94 mother group O/infant group A (O-A), 16 mother group O/infant group B (O-B)) in which the cord blood elution test was positive. The elution test was graded as weakly positive or strongly positive. A control group consisted of 110 mother group O/infant group O (O-O) deliveries who were born immediately before or after the index case. All were Rhesus compatible The incidence and severity (peak serum bilirubin concentration) of clinically detectable jaundice was determined for each group. Statistical comparisons were made using the χ^2 and Wilcoxon's rank sum test as appropriate. The protocol for treatment of the jaundice was identical for the two groups. This, therefore, could not have been a confounding variable.

Results

Information about sex, gestation, birth weight, method of delivery, and method of feeding for each group is shown in table 1. Table 2 shows data about jaundice. The difference in the incidence of jaundice between the two groups was not significant ($p>0·1$) The peak serum bilirubin concentration of those who were jaundiced did not differ significantly between the two groups The incidence and severity of jaundice in the O–A and O–B groups did not differ significantly.

Table 1 *Details of infants studied*

	ABO incompatible group (n=110)	*Control group (n=110)*
Sex.		
Male	53	59
Female	57	51
Mean (SD) gestation (weeks)	39·7 (0·2)	39·7 (0·2)
Mean (SD) birth weight (g)	3400 (50)	3350 (50)
Method of delivery·		
Vaginal	89	83
Breech	1	2
Caesarean section	12	17
Instrumental	8	8
Method of feeding		
Breast	29	40
Bottle	81	70

Table 2 *Details of jaundice in the two groups of infants*

	ABO incompatible group (n=110)	*Control group (n=110)*
No with clinically detectable jaundice		
Whole group	29 (26%)	18 (16%)
O–A group	26	
O–B group	3	
Median (range) peak serum bilirubin concentration of jaundiced babies (µmol/l)	*(n=29)*	*(n=18)*
Whole group	171 (11–282)	190 (159–295)
O–A group	166 (111–282)	
O–B group	198 (149–228)	

The direct Coombs test was positive in 36 (33%) of the study cases. Fourteen (39%) became clinically jaundiced with a peak serum bilirubin concentration range of 111–236 µmol/l (median 162 µmol/l). A higher proportion of patients who were Coombs positive became jaundiced (14 out of 36, 39%) than those who were Coombs negative (15 out of 74, 20%). This did not achieve significance ($0·1>p>0·05$). When compared with the control group, however, jaundice occurred significantly more often in Coombs positive patients ($p<0·01$). There was no significant difference in severity from the control group.

Similarly, jaundice occurred more often in patients with a strongly positive elution test (13 out of 37, 35%) than in those with a weakly positive elution test (16 out of 73, 22%). This did not achieve significance ($0·1>p>0·05$) but did do so when those with a strongly positive elution test were compared with the control group ($p<0·05$). Again, there was no significant difference in severity from the control group.

Oxytocin was used in 28 (16 cases, 12 controls) of 116 deliveries (58 cases, 58 controls). In the remainder this information was not recorded in the labour ward register. The use of oxytocin did not affect the incidence of jaundice.

None of the infants born at term became sufficiently anaemic to require a top up transfusion.

Discussion

The effects of ABO haemolytic disease have been described as varying from a subclinical compensated haemolytic process[3] to hydrops fetalis.[4] The reasons for this variable clinical expression are not clear. One reason may be that the A and B antigens are expressed more weakly on fetal cells than on adult cells.[5] The strength of expression increases with gestation.

In this group of patients ABO incompatibility (as defined by a positive elution test) has not been a clinical problem. Perhaps a less sensitive screening test than that presently used is required. Jaundice was more likely to occur in those with a positive Coombs test or a strongly positive elution test but it was no more severe than in the control group.

On the basis of these findings we believe that routine screening for ABO incompatibility using the elution test is of no clinical benefit. In an individual case, however, a positive Coombs test or a strongly positive elution test may be useful in predicting the occurrence of jaundice.

We acknowledge the work of the haematology laboratory, Fazakerley Hospital, without which this study would not have been possible

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Ataxic cerebral palsy and genetic predisposition

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SUMMARY It was calculated that in the 962 family members of 36 patients with ataxic cerebral palsy there were 75 (8%) with a history of neurodevelopmental disorder and 31 (3%) with a major congenital malformation. This was not significantly greater than expected, and does not support the hypothesis of a genetic non-Mendelian role in the aetiology of ataxic cerebral palsy.

It has been suggested that a genetic non-Mendelian influence may play a part in a multifactorial aetiology in cerebral palsy. This gives rise to a constitutional vulnerability to several risk factors and a predisposition to neural tissue damage, and is expressed as an increase in neurodevelopmental disability and major congenital malformation in the near relatives.[1 2] In ataxic cerebral palsy, the least common of the syndromes of cerebral palsy, the infants are usually of normal birth weight with a prenatal origin of the condition.[3] The family histories of a population with this disorder were therefore examined for the frequency of neurodevelopmental disability and major congenital malformation in order to assess the role of a genetic influence in aetiology.

Subjects and methods

Cerebral palsy is defined as a group of disorders of movement and posture due to a non-progressive defect or lesion of the developing brain.[4] When this disorder is an ataxia, which is not primarily due to weakness, spasticity, dystonia, or choreoathetosis, it is termed ataxic cerebral palsy.

Thirty six cases of ataxic cerebral palsy were ascertained from the West Australian cerebral palsy register and from the records of the Spastics Welfare Association of Western Australia. Each case was individually examined to ensure they fulfilled the criteria for diagnosis. All were older than 5 years of age and had histories consistent with a non-progressive disorder. The number of cases of ataxic cerebral palsy ascertained represented 72% of the metropolitan population (details to be published elsewhere).

A history of neurodevelopmental disability or major congenital malformation in the parents, aunts and uncles, first cousins, siblings, and children of siblings, was recorded. The categories of neurodevelopmental disability used are listed in the table. Details of these were checked against the medical records of several institutions and by correspondence with the relevant personnel who were concerned.

Results

Out of a total of 962 people on whom information was sought, 75 (8%) had neurodevelopmental dis-

Table *Categories of neurodevelopmental disability*

Intellectual handicap
Cerebral palsy
Language delay or disorder ascertained by specialist consultation
Epilepsy of unknown origin
Congenital hearing loss
Severe visual handicap
Congenital strabismus
Special educational requirements–remedial teaching, special class or school (where the reason was not considered to be primarily socioemotional)

abilities and 31 (3%) had major congenital malformations. In a few instances (nine) the history of a relative was uncertain or could not be verified, and they were removed from the calculations.

There were two sisters with a similar non-progressive ataxic disorder whose histories and computed tomograms could have been consistent with Joubert's syndrome, and one boy whose mother had a similar condition.

Discussion

The prevalence of neurodevelopmental disability in a general population similar to the one reported here and using similar criteria, has been reported to be 12–16%.[5] An increased frequency of neurodevelopmental disability in the direct families and near relatives of those with ataxic cerebral palsy could thus not be shown. The figure of 8% is somewhat low, and this may have been due to underascertainment as, although a thorough history was taken and parents were asked to contact their relatives, a disability may not have been admitted. However, about 100 cases would have to be missed to achieve an 18% incidence of neurodevelopmental disability and it is most unlikely that those numbers were missed. It would have been more satisfactory if the frequency of neurodevelopmental disability in the local population had been known.

The figures for 1980–3 for the percentage of Western Australian births with a major congenital malformation ranges from 3·2% to 4·2% (Western Australian Congenital Malformations Register Annual Report, 1984), a similar figure to that found in the current study.

Ingram,[6] in his study of ataxic cerebral palsy, reported a high proportion of near relatives with different types of neurological disorder, and Monreal in a clinic population study of cerebral palsied children stated that there was an unusual number of relatives with cerebral palsy, mental retardation, and seizures.[2] The methods used in those two studies differ, however, from those used in this report, and the results are not really comparable.

This study of a large proportion of a metropolitan population of patients with ataxic cerebral palsy does not support a genetic non-Mendelian influence in the aetiology of this heterogeneous disorder.

I am indebted to Dr Fiona Stanley and Linda Watson for access to the West Australian cerebral palsy register, the Spastics Welfare Association of Western Australia, and to Carolyn Ebell for preparation of the manuscript

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Have school entry medicals had their day?

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SUMMARY Examination of the school health records of 1033 primary school entrants showed that there was a high level of preschool surveillance by health visitors and that most problems recorded at school entry medical examinations were already known to another professional.

It is policy in Northern Ireland that all children commencing primary school are given a school entry medical examination. There are widely differing views held about the value of these routine examinations. Some believe they are of little value[1] while others consider them to be of special importance.[2] The aims of this study were firstly to determine the number of children with records of preschool surveillance by health visitors and secondly to determine the number and types of problems found at the school entry medical examination and how these were dealt with.

Methods

The study population included children who in September 1986 commenced ordinary primary schools in the health care district of Newtownabbey. The district has a population of 72 000 (of which 14 000 are schoolchildren) and is a largely urban community close to Belfast.

When a child starts school the health visitor records should be transferred to the school health service. At the school entry medical examination each child has a general physical examination by the school doctor and height, weight, and visual acuity measured by the school nurse. Neurodevelopmental screening tests are not routinely carried out in Newtownabbey. In some parts of the district the local speech therapist visits primary schools and sees children at their parents or teachers request. Hearing is screened by the educational audiology service. The school health record for each child should therefore consist of the health visitor records and notes made at the school entry medical examination.

The children who started at primary school were identified from the school rolls. Their school health records were retrospectively examined to ascertain the availability of health visitor records, recorded contacts by the health visitor since the child was aged 3, whether a school entry medical examination was done during the school year September 1986–June 1987, the nature of problems detected at the examination, and how these were dealt with (dental problems excluded). A problem was considered 'new' if it was found for the first time or, had been previously known but had recurred. A problem was considered 'already known' if another health professional was dealing with it. New problems that were referred were followed up by contacting the relevant health professional and ascertaining what action had been taken. (The exception to this was in the case of referrals to an optician when parents were contacted about the outcome.)

Results

Of the 1048 children in the study population, 12 were excluded as they had moved out of the district therefore their records had been transferred. The records of three children could not be traced, this left 1033 school health records in the study.

The health visitor records were available for 951 children (92%). The records showed that 899 children had been seen by a health visitor since 3 years of age of whom 858 (83% of 1033) had a developmental check recorded (usually in the form of a standard questionnaire). In most cases hearing and vision were not formally tested by health visitors.

Of the 1033 children, 985 (95%) had a school entry medical examination. A total of 613 problems were recorded in 457 children (that is, 46% of the children seen had at least one problem); 382 problems (62%) were already known to another professional; 231 (38%) were new. Of the 231 new problems almost half (115) did not require referral, the remaining 116 were referred to another professional. Details of the types of problems and referral patterns are shown in table 1.

The six commonest new problems are shown in table 2. They represent 83% of all the new problems found. It is apparent that had children been screened for only four problems (vision/squint, speech, hearing, and short stature) 69% of detected new problems would have been found.

Of the 116 new problems that were referred, 90

Table 1 *Types of problems and referral patterns in 457 children*

Type of problem	*Total No (%)*	*No of already known problems*	*No of new problems*	*No of new problems referred*
Physical*	304 (50)	224	80	45
Vision/squint	116 (19)	38	78	49
Hearing	93 (15)	64	29	13
Speech	75 (12)	45	30	6
Behaviour	14 (2)	4	10	1
Learning difficulty	6 (1)	4	2	0
Social	5 (<1)	3	2	2
Total	613	382	231	116

*Physical problems other than vision, hearing, speech

Table 2 *Commonest new problems*

Type of new problem	*No of new problems*
Vision/squint	78
Speech	30
Hearing	29
Short stature	22
Cardiovascular	17
Undescended testes	16
Total	192

(78%) referral appointments were kept. Vision, hearing, and speech problems accounted for well over half (59%) of new problems referred. Of those seen at referral, 51 problems (57%) required some sort of intervention.

Discussion

The results of this study show a high level of preschool surveillance by health visitors in the district. Although 46% of the children seen for a school entry medical examination were recorded to have a problem, 62% of these problems were already known to another professional. Other studies also report low yields of new problems.[3] [4] In this study most new problems could have been found by screening tests that need not involve a doctor. This suggests that medical time would be better spent on selected children. It has been shown that parents like their children to have school medical examinations—parental opposition to a selective policy might therefore be anticipated.[5] A practicable solution would be for the school nurse to screen children and refer those she feels require further assessment to the school doctor. This would allow more time for comprehensive assessments of selected children. As many school doctors also work in community child health clinics more time could be given to preschool surveillance work.

Other alternatives to routine school entry medical examinations have been put forward.[3] [6] Any new system will require evaluation before it can be proved to be better than the present one. It does seem, however, that little is being achieved by unselective medicals and that a change is long overdue.

I thank those who cooperated in this study particularly the general practitioners, also my senior colleagues who gave constructive advice in the preparation of this paper

The results of this study were presented at Part 2 of the course for Community Health Doctors at the Royal Institute of Public Health and Hygiene, Portland Place, London, in October 1987

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Glucagon for hypoglycaemia in infants small for gestational age

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SUMMARY Twenty five infants who were small for gestational age received glucagon (0·5 mg/day by continuous infusion) in the treatment of hypoglycaemia. Twenty responded within three hours with a rise in blood glucose concentration to above 4 mmol/l. Five subjects subsequently required hydrocortisone to maintain glucose concentrations. Rebound hypoglycaemia occurred in nine infants after rapid discontinuation of glucagon or interruption of the intravenous infusions. Response was poor after maternal β blockade.

Hypoglycaemia is a common problem in the infant who is small for gestational age. Many paediatricians use corticosteroids if the hypoglycaemia fails to respond to high caloric intake. Although glucagon is often used for the management of hypoglycaemia in the infant of the diabetic mother, in a recent textbook of neonatology no reference is made to its use in infants who are small for gestational age.[1] A recent paper did, however, describe low glucagon concentrations in a group of hypoglycaemic term infants, successfully treated with a single intravenous bolus of glucagon.[2] For several years we have used a continuous glucagon infusion as the first line of treatment if hypoglycaemia persists despite high energy oral feeds and concentrated solutions of intravenous dextrose. We report here our experience over the last five years.

Patients and methods

Patients were all infants born at Aberdeen Maternity Hospital between January 1982 and December 1986 whose birth weight was below the 5th centile for gestational age, and in whom it had not been possible to maintain capillary blood glucose concentration above 2 mmol/l by the use of intravenous dextrose 12·5% solution at appropriate volumes (supplying 5·5 mg/kg/minute of glucose on day 1) and a bolus of dextrose 0·2 g/kg together with frequent feeds of high energy milk (Prematalac, Cow and Gate).

Glucagon was infused continuously in 10% dextrose at a standard dosage of 0·5 mg/day and increased as necessary to maintain capillary blood glucose concentration at or above 4 mmol/l (BM Test, Glycaemie) as in our protocol for management of the infant of the diabetic mother.[3]

Results

A total of 25 babies were treated during the study period of whom nine were preterm (range 33–40 weeks' gestation). Mean birth weight was 1872 g (range 730–2300). Seven mothers had pre-eclampsia, three essential hypertension, one systemic lupus erythematosis, and one cryptogenic chronic renal failure. Three were receiving β blockers (metoprolol or atenolol). Irritability was present in seven infants. Mean age at starting glucagon was 15·7 hours (range 3–41).

In 23 cases the blood glucose concentration rose above 4 mmol/l on the initial dosage of 0·5 mg/day, in 20 within three hours (see figure). Maximum daily infusion rate of glucagon was 0·5 mg in 16 infants, 1 mg in five, and greater in four, to a maximum of 20 mg/day in one case. Mean duration of treatment was 8[illegible] hours (range six hours to three weeks). Five infants developed hyperglycaemia (a glucose concentration >10 mmol/l), which responded to reduction of the infusion rate. Hypoglycaemia recurred in three infants after interruption of the infusion, and in a further six when the glucagon dosage was rapidly decreased after an adequate initial response. In only three of the latter was it possible to restore blood glucose concentrations by reintroducing glucagon. In the other three, hydrocortisone was required. Steroids were given in a further two cases (at 30 minutes and six hours respectively after

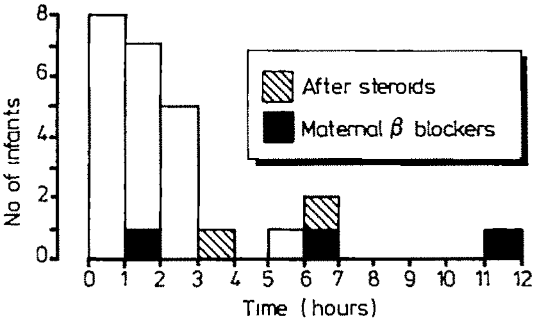

Figure *Time until blood glucose concentration was ≥ 4 mmol/l.*

commencing glucagon) because of failure of initial response and in three cases of partial response with prolonged marginal hypoglycaemia, at 11 hours, 70 hours, and nine days. Hyperinsulinism lasting six weeks was found in the infant who received steroids after 30 minutes. Of the three infants whose mothers received β blockers, two showed delayed response to glucagon at seven and 12 hours respectively, although the third infant responded within two hours (figure).

OUTCOME

Two infants died from unrelated causes. Necrotising enterocolitis developed during treatment in one infant who had been badly asphyxiated and whose mother was treated with metoprolol. In this case hypoglycaemia was refractory and despite 20 mg/day of glucagon, intravenous hyperalimentation, and corticosteroid the blood glucose concentration was barely maintained at 2 mmol/l. Low thyroxine and cortisol concentrations were found; these eventually resolved spontaneously. There was one case of rectal bleeding with proctoscopic appearances of cows' milk protein intolerance, and another of mild diarrhoea. Two infants became transiently thrombocytopenic and in one of these there was unexplained hyponatraemia. Of the four infants who developed convulsions, two had been badly asphyxiated and one had suffered intracranial haemorrhage. In only one case might hypoglycaemia have been responsible for the convulsions

At follow up 20 infants are normal and three developmentally delayed. Of the abnormal children, however, one has congenital rubella syndrome and one suffered intracranial haemorrhage. The third is the child described above, with refractory hypoglycaemia. Four otherwise normal children have squints.

Discussion

The causes of hypoglycaemia in infants who are small for gestational age remain uncertain. Reduction in hepatic glycogen stores is one factor, but reduced gluconeogenesis due to delayed maturation of phosphoenol pyruvate carboxykinase may also be important.[4] Although an occasional infant may show relatively low glucagon concentrations,[2] Mestyan *et al* have shown a degree of resistance to the gluconeogenic effects of glucagon in hypoglycaemic infants who were small for gestational age,[5] suggesting that supraphysiological concentrations may be necessary in these babies.

We have used a continuous infusion of glucagon, in a dosage similar to that shown by Mestyan *et al* to effect a rise, albeit blunted, in blood glucose in hypoglycaemic infants who were small for gestational age (0·2 μg/kg/min). As 28% of our subjects required an increase in glucagon infusion to above 0·5 mg/day, it is likely that this is near the minimum effective dose. We believe it to be more physiological than the use of a single bolus of 0·2 mg/kg as advocated by Mehta *et al* as, in adults and older children, bolus doses of only 1 mg are often associated with vomiting. Mehta *et al* report a sustained glycaemic effect in a small group of term infants treated with a single bolus. Unfortunately it is not possible to compare these studies as his group of larger babies with low glucagon concentrations may well represent a different population from our own group of low birthweight infants who were small for gestational age, and the course of the only infant weighing less than 2500 g is not fully documented. Further studies in infants of low birth weight would be of value.

The poor response in infants born to mothers receiving β blockers suggests that these babies may be particularly resistant to the effect of glucagon. Glucagon releases catecholamines from the adrenal medulla,[6] and this may be an important aspect of its therapeutic action.

Our experience with a heterogeneous group of patients shows that intravenous glucagon is effective in the infant who is small for gestational age, in that adequate blood glucose concentrations were obtained in 80% of babies within three hours of starting treatment. We suggest that in those infants who respond, glucagon be discontinued slowly (over 24 hours or more), and that infusions be rapidly resited during treatment, as rebound hypoglycaemia may be resistant to treatment. If response does not occur within four hours we recommend the early addition of hydrocortisone as late response is uncommon. Similarly, if there is no response to 2 mg/day, further dosage increase is unlikely to be of value. Resistant hypoglycaemia is particularly likely after β blockade.

We believe that glucagon is a safe and effective treatment for hypoglycaemia in the infant who is small for gestational age, enabling early introduction of oral feeds and avoiding the need for highly concentrated dextrose infusions.

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Acute pneumonia in Zimbabwe: bacterial isolates by lung aspiration

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SUMMARY Forty children, aged 2 months to 11 years, with severe acute pneumonia were investigated by needle aspiration of the lung. Fourteen organisms were isolated in only 13 patients. *Streptococcus pneumoniae* was isolated in six patients, *Staphylococcus aureus* in three, and *Haemophilus influenzae* in two. Two patients had mixed organisms.

Severe acute lower respiratory infection is common in developing countries and is a major cause of mortality. Studies from some developing countries indicate a high prevalence of bacteria in the aetiology of pneumonia in hospitalised children.[1 2] This may not be universally the case. The present study was aimed at determining whether bacteria are the dominant cause of pneumonia in children in Zimbabwe as has been found in some developing countries.

Patients and methods

The study was conducted between February and August 1987. All children admitted under one of the three paediatric firms with severe pneumonia were investigated by needle aspiration if they had not received any antibiotics before admission. The needle aspiration was performed according to a standard method with slight modification.[3] The aspirate was cultured on blood and chocolate agar, and tryptose phosphate or brain-heart infusion broth. The positive growths were indentified by standard bacteriological methods. Initially negative cultures were subcultured for 10 days.

In the period under consideration 123 children were discharged with a final diagnosis of either lobar pneumonia or bronchopneumonia. Of these 40 qualified for lung aspiration and had the procedure carried out. All were between the ages of 2 months and 11 years. All had a history of respiratory infection of less than five days' duration. The extent of the consolidation was determined by physical examination and confirmed on a chest radiograph and involved at least a whole lobe.

Results

Fourteen bacterial organisms were isolated by lung aspiration from 13 children amounting to a positive isolation rate of 32·5%. Of the single isolates the dominant organism was *Streptococcus pneumoniae,* which was isolated in six patients, followed by *Staphylococcus aureus* in three, and *Haemophilus influenzae* in two. Two patients had mixed organisms, one with *S pneumoniae* and *H influenzae* and another with *S aureus* and *Mycobacterium tuberculosis.* The *M tuberculosis* was isolated from sputum culture.

There were no deaths attributable to lung aspiration. The only death in the series was an 18 month old child with severe kwashiokor and right upper lobe pneumonia due to *H influenzae* and large intracerebral abscess presumably due to the same organism. One patient had slight haemoptysis that cleared within 30 minutes, and another had a small pneumothorax that cleared spontaneously.

Discussion

Needle aspiration of the lung is the only definitive way of establishing the bacterial organism responsible for acute pneumonia. Studies from developing countries using this technique have established beyond doubt the dominant role of bacteria in the aetiology of acute pneumonia in hospitalised children.[1 2 4] This, together with widespread malnutrition, had led to the almost universal use of antibiotics, often in broad spectrum combinations, in the treatment of most children with lower respiratory tract infection in and outside hospitals even when the clinical findings strongly suggest a viral aetiology. This practice has serious economic consequences for these poorer countries considering the large numbers of children seen with respiratory infections in and outside hospitals. It no doubt reflects the frustration of the doctor confronted with inadequately investigated lower respiratory infection in a sick child who is often in severe respiratory distress. Not least is the problem of emergence of resistant bacterial strains where antibiotics are used widely. The paucity of information from many developing countries regarding the aetiology of acute lower respiratory infection in children makes rationalisation of treatment difficult.

The result of this small series suggest that bacterial infection is not the most common cause of pneumonia in Zimbabwe in contrast with other developing countries such as Nigeria,[1] Papua New Guinea,[2] and Chile[4] where most pneumonias in hospitalised children are caused by bacteria. Comparing these countries with high bacterial prevalence important regional differences in the bacteriological pattern become apparent. For instance, in Papua New Guinea *H influenzae* dominates over *S pneumoniae* as the cause of pneumonia in children and *S aureus* was conspicious by its total absence, whereas in Santiago, Chile, *S aureus* was by far the commonest organism isolated. In Nigeria *S pneumoniae* accounted for 62% of the isolates.

It is therefore clear that information obtained in one region may not necessarily be applicable to other areas. To be able to rationalise treatment and make recommendations knowledge of the bacteriological pattern and bacterial sensitivities in the particular area is essential. Identification of areas of low bacterial prevalence would also mean for governments in those areas more money spent on means of providing supportive care in hospitals if there is to be any substantial reduction in mortality due to lower respiratory infections in children, particularly in infants.

The value of lung aspiration in acute lower respiratory infection is beyond question. The technique is easy and safe and undoubtedly superior to sputum, nose and throat swabs, and aspirates from the tracheobronchial tree.[1 2 5] It enables not only the exact identification of the causative bacterial organism but also the determination and monitoring of antibiotic sensitivity. The morbidity of the procedure is small and usually minor as is evident from this study and those of others.[1 2 4] In children with negative bacterial growth, which implies in most cases acute viral infection, the therapeutic emphasis will have a shift towards supportive care if these often very sick children are to survive.

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Disseminated BCG in HIV infection

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SUMMARY A boy, born to a mother with AIDS related complex, was immunised with BCG on the 10th day of life. At the age of 4 months he presented with a local enlarged lymph node, fever, hypotonia, and diarrhoea. *Mycobacterium bovis,* BCG strain, was grown from the lymph node and cerebrospinal fluid; this proved dissemination.

The increasing prevalence of HIV infection in children, associated with immune deficiency, has led to concern about the efficacy and complications of immunisation among these children.[1 2] The problem of whether children infected with HIV should receive live vaccines is complex: the risk of vaccination must be balanced against the risk of infection in the non-vaccinated child.

There is evidence that HIV infection is responsible for the increased frequency of infection with tuberculosis and for morbidity with this micro-organism.[3] Patients with AIDS and tuberculosis are more likely to have extrapulmonary disease,[4] although bacteraemia in disseminated *Mycobacterium tuberculosis* is rare. In patients with AIDS related complex infection due to *M tuberculosis* is of poor prognosis, accelerating the transition to AIDS even if tuberculosis is only restricted to the lungs.[4]

These problems with HIV infection and tuberculosis prompted us to explore the use of BCG vaccine in children who were HIV positive. Some cases of local adenitis after BCG immunisation have been reported.[1] Although a few case reports suggest a generalised infection due to BCG in patients infected with HIV, dissemination has never been clearly proved, except for the isolation of *M bovis* in one reported case from blood culture in an adult with AIDS and Kaposi's sarcoma.[5]

We report here a case of disseminated infection caused by *M bovis* after BCG vaccination in an infant infected with HIV who presented with generalised lymphadenopathy, hypotonia, fever, diarrhoea, and raised liver enzyme activities.

Case report

A boy, born in Zaire to a mother with AIDS related complex, was immunised with BCG on the 10th day of life. Between the age of 1 and 2 months, he presented with repeated urinary tract infections, mucocutaneous candidiasis, and high fever. He was transferred to our hospital at the age of 4 months, for persistent fever, weakness, fatigue, anorexia, and diarrhoea.

On admission, he was an ill looking baby with a body temperature of 38·8°C His weight was 4600 g (10th centile), height 58 cm (5th centile), and head circumference 39·5 cm (5th centile). He had an enlarged lymph node in the left axilla (diameter >2 cm) near the BCG vaccination site, hepatosplenomegaly, and hypotonia. The erythrocyte sedimentation rate was >150 mm in the first hour, fibrinogen concentration 2·86 g/l, and the C reactive protein concentration 0·246 g/l. His white cell count was 5×10^9/l (30% lymphocytes) and haemoglobin concentration 80 g/l. His liver enzyme activities were raised: serum aspartate transaminase, 110 IU/l (normal <40); serum alanine transaminase, 50 IU/l (normal <40); alkaline phosphatase, 385 IU/l (normal range 80–280); lactate dehydrogenase, 1200 IU/l (normal range 140–300); and γ glutamyl transferase, 1300 IU/l. Plasma gammaglobulin concentration was 65 g/l and the T4/T8 ratio was 1·4 (T4, $0{\cdot}269\times10^9$/l; T8, $0{\cdot}190\times10^9$/l). The in vitro response of lymphocytes to mitogens (phytohaemagglutinin, pokeweed, concanavalin A), and OKT3 was extremely reduced.

Although antibodies against HIV-1 were not detected in the serum either by two commercial enzyme linked immunoadsorbent assays (ELISA) (Pasteur production and Abbott env/core recombinant EIA) or by immunofluorescence, further investigations were performed as the mother was known to be seropositive. Another ELISA test (Wellcome) was found to give a weak positive result and Western blot analysis showed a low level of antibodies against GP 120. Moreover, HIV-1 antigen was detected repeatedly in six serum samples from the patient (Abbott HTLV-III antigen EIA). A search for infection showed *Candida albicans* and enterococci in a throat swab, but no bacterial infection was found in blood, stools, or urine. No viral, fungal, or protozoal infection was found. Culture of cerebrospinal fluid, however, grew colonies of an acid fast bacillus, identified as *M bovis,* BCG strain. *M bovis* could not be isolated from blood or from a nasogastric tube, but was grown in pus from the enlarged lymph node. A chest radiograph was normal apart from showing an enlarged heart. Cardiac ultrasonography excluded a pericardial effusion. Examination of the optic fundus, electroencephalography, and cerebral ultrasonography gave normal results. Abdominal ultrasound showed normal kidneys but the liver was appreciably enlarged. A liver biopsy was attempted but unfortunately failed to produce liver tissue.

The child was treated with rifampicin 15 mg/kg/day, isoniazid 10 mg/kg/day, and ethambutol 20 mg/kg/day. His general condition improved dramatically and he became afebrile on the third day of treatment, and the local inflammatory signs disappeared around the affected lymph node. The results of his blood tests also showed a rapid improvement: the erythrocyte sedimentation rate fell from 150 mm in the first hour to 50 mm on the fifth day of treatment, the liver enzymes returned to normal values. The in vitro response of lymphocytes to mitogens remained low, however, and the T4/T8 ratio fell to 0·33 at the age of 5 months (T4, $0{\cdot}072\times10^9$/l; T8, $0{\cdot}215\times10^9$/l). Hepatosplenomegaly became more prominent and hypotonia persisted, although it was less pronounced. The child returned to Zaire at the age of 5 months. He died two months later, probably from bacterial infection.

Discussion

The World Health Organisation recommends avoidance of the use of BCG in children infected with HIV who have symptoms as the efficacy is disputed in these children,[6] and because dissemination has been described in an adult patient.[5] In the case reported here of *M bovis* dissemination, the infant who was infected with HIV was vaccinated on the 10th day of life, before he had any clinical symptoms of HIV infection. Dissemination was proved in our patient by culture of *M bovis*, BCG strain, in the cerebrospinal fluid and in the lymph node (local inflammation due to BCG).

Although tuberculosis represents a real problem in Africa, and despite the fact that the frequency and the gravity of tuberculosis is increased in subjects infected with HIV[3] with a great propensity for extension to extrapulmonary sites,[4] our observation clearly shows that it is not advisable to vaccinate infants born to mothers infected with HIV with BCG, unless HIV infection can be ruled out in the child.

We would like to thank Dr R Coosemans for referring the patient as well as Professor J Prignot and Dr I Hann for their help during preparation of the manuscript

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Thoracic neuroblastoma presenting as a cystic hygroma

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SUMMARY A case of thoracic neuroblastoma with extension into the supraclavicular fossa is described. By physical examination and ultrasound the patient was thought to have a cystic hygroma with mediastinal extension. A 'cystic' neck mass may be the initial presentation of a mediastinal neuroblastoma.

Neuroblastoma is the third most common tumour of childhood.[1] The initial clinical presentation of the tumour is remarkable for its protean manifestations. In addition to the frequent finding of a firm mass on physical examination of the child, the initial presentation also may be characterised by symptoms and findings related to metastatic spread of the tumour or its metabolic effects.

We report a case of an infant with mild respiratory distress and a neck mass that felt like a cyst located in the supraclavicular area. The ultrasound findings supported the diagnosis of cystic hygroma. On pathological examination it was found that the presumed cystic mass was a primitive neuroblastoma with haemorrhage and necrosis. There have been previous reports of abdominal neuroblastoma diagnosed preoperatively as cystic masses.[2 3] A cystic neck mass therefore can be added to the list of presentations of thoracic neuroblastoma.[4]

Case report

A 6 month old boy was admitted to hospital with fever and congestion. A chest radiograph showed right upper lobe consolidation possibly a mass. On physical examination he had right supraclavicular adenopathy. The patient was transferred to the Children's Hospital of Eastern North Carolina because of the possibility of a chest tumour.

The patient was examined and found to have several small (1–2 cm) firm, nodular like masses as well as several small cystic masses in the right supraclavicular area. The total mass was about 3×3 cm and transilluminated The rest of the physical examination was normal A repeat radiograph showed the previously described extrapulmonary mass with deviation of the trachea to the left, indicating mass effect in the mediastinum (fig 1). Ultrasound of the neck showed a supraclavicular mass with mediastinal extension consisting of multiple separate fluid filled spaces with echogenic material within some of the cysts (fig 2). The findings were compatible with a cystic hygroma, or, less likely a cystic teratoma.

The patient was admitted three weeks later for excision of the cystic hygroma. At surgery multiple cystic like nodules were removed from the right supraclavicular fossa. Grossly the tumour nodules were lobulated and contained grey, firm, homogeneous areas on cut section. Extensive areas were haemorrhagic and necrotic. Microscopically the neoplasm was highly cellular and consisted of cells slightly larger than mature lymphocytes. Cells were present in sheets and often clustered about a central area of eosinophilic, filamentous material (Homer Wright rosettes). This filamentous material and the individual cells stained strongly with neurofilament and neuron specific enolase. Mitoses were frequent. Electron microscopic examination was remarkable for glycogen and numerous electron dense neurosecretory type granules, features characteristic of neuroblastoma.

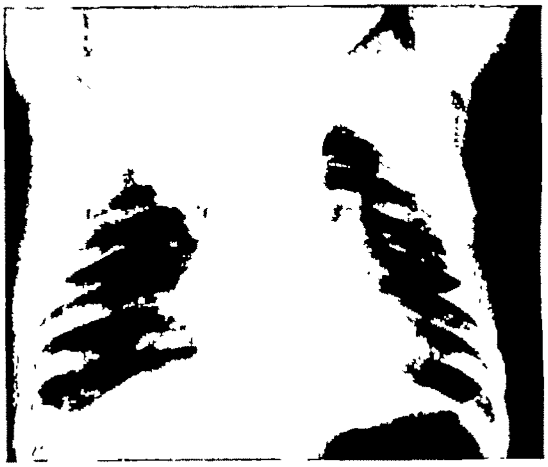

Fig 1 *A frontal radiograph of the chest showing a soft tissue mass displacing the trachea both within the neck and within the thorax which on a lateral radiograph (not included) was displacing the trachea slightly anteriorly. No calcification is obvious on the plain films.*

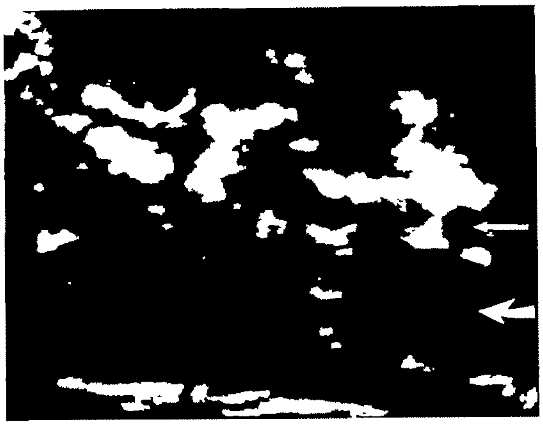

Fig 2 *A transverse ultrasound study of the neck showing a mass consisting of multiple fluid filled spaces as evidenced by the lack of internal echoes, strong backwall, and increased through transmission of sound. There are solid elements within some of the fluid filled spaces. Thick arrow indicates jugular vein, thin arrow indicates carotid artery*

One week later the patient underwent a thoracotomy to debulk the remaining intrathoracic tumour. At surgery a large tumour posterior to the oesophagus was dissected from the superior vena cava, inominate artery and vein, as well as carotid and subclavian arteries. The tumour was found to extend into the vertebral foramina T4, T5, T6, and T8 and small remnants were left. The pathology of the tumour was similar to the previous biopsy specimen and showed a neuroblastoma with rare ganglionic differentiation.

Preoperatively the urinary vanillylmandelic acid concentration was 103 μg/mg creatinine (upper limit of normal, 15 μg) and the homovanillic acid concentration was 8 μg/mg creatinine (upper limit of normal, 37 μg). The postoperative metastatic workup, which included a bone marrow biopsy, ultrasound of the abdomen, a skeletal survey and bone scan, gave negative results for tumour.

The patient received five courses of chemotherapy given every three weeks; this consisted of daily oral cyclophosphamide (150 mg/m^2) for seven days followed on day eight by adriamycin (35 mg/m^2). Complete re-evaluation after five courses of treatment showed that the patient had no evidence of tumour. He has had no recurrence of the tumour in the 18 months since diagnosis.

Discussion

Our case is interesting from several aspects of differential diagnosis. Because of the location of the cystic like mass in the supraclavicular area, the patient was thought to have a cystic hygroma.[5] Thoracic extension of the neck mass occurs in 10% of the cases.[6] The sonographic findings in our case appeared to confirm the cystic nature of the mass. The echogenic areas within the mass were compatible with lymphangiomatous malformations. Another diagnostic consideration was a cervical teratoma, which can cause respiratory distress by tracheal compression.

There have been reports of cystic abdominal masses diagnosed by ultrasound, which at surgery were found to be neuroblastomas. In these cases the cystic masses were thought preoperatively to represent cystic changes in the adrenal gland resulting from haemorrhage.[2 3] Biopsy specimens taken from the cases reported have shown, like those from our patient, haemorrhage, necrosis, and a variable amount of microcystic transformation within the neuroblastoma.

The clinical presentation of neuroblastoma is remarkable for its variety.[4] Patients with thoracic neuroblastoma may present with severe respiratory distress due to tracheal compression from the tumour. Neurologic dysfunction due to extension of the tumour into the vertebral canal and Horner's syndrome due to involvement of the cervical ganglia are other clinical presentations in the thorax.[4] Occasionally a patient is found to have a thoracic neuroblastoma on a routine chest radiograph. Our case adds another clinical presentation for thoracic neuroblastoma, namely a cystic like neck mass. When encountering children with cystic neck masses containing nodular (presumed lymphatic) tissue components and notable extension into the mediastinum one should consider neuroblastoma.

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Looking back

Great Ormond Street 50 years ago

DOUGLAS GAIRDNER

I was appointed house physician at The Hospital for Sick Children in 1937. In retrospect I can see that I was there at a very particular time in the hospital's history, because 1937 was to mark the end of an era. A decade or so before, the fame of Great Ormond Street had depended on a generation of physicians of the calibre of Still, Garrod, Batten, and Poynton. But the staffing of the hospital and the way the work on the medical side was carried out had changed but little in the 20 years between the wars Change, however, was afoot and by the following year, 1938, the picture was at last beginning to alter, as will be explained.

I was one of only two house physicians, and my appointment was to Drs E A Cockayne and Donald Paterson. These two gentlemen had not been on speaking terms for years. So they had come to a tacit agreement whereby each took it in turn to appoint the shared house physician.

House physician jobs at Great Ormond Street were highly competitive, and it was understood that to stand much chance of success an applicant should have the Membership of the Royal College of Physicians, and should also demonstrate his keenness by having made one or more previous applications. I did not have the Membership, and indeed was very junior, having been qualified less than a year. However, I did possess one crucial asset—I came from the right medical school, the Middlesex, for Dr Cockayne, whose turn it was to appoint, was 'on' at the Middlesex as a general physician. Hospital chauvinism was a powerful force and to it, unworthily, I owe my entry to Great Ormond Street

The two chiefs I found myself working for each had a ward of about 26 cots, but the two firms had little else in common. The senior of the two, Dr Cockayne—Cocky—was a shy eccentric; it was my loss that I never felt able to get onto his wavelength, or to know how to respond to the curious little giggles which accompanied the remarks that he would drop, often after a disconcertingly long silence, in the course of his twice weekly ward round. But my successor, Dick Bonham-Carter, became a devotee of his, and says: 'Cockayne was an Edwardian bachelor, who did not care for women. This attitude was compounded by the fact that he had to teach female medical students from the Royal Free Hospital at Great Ormond Street. Furthermore he had had rooms in Lancaster Gate when the building had been bought by London University and turned into a female students' hostel. He was very fond of children, but his life and his original work were devoted to genetics His OBE was awarded for his work in entomology; he was President of the Royal Entomological Society, having made his name by cataloguing the Rothschild's collection of British moths, a genetic study. In human genetics his *Inherited Diseases of the Skin and Appendages* was a classic. His knowledge and memory were remarkable. A physician at Hammersmith Hospital rang up to ask me to tell Dr Cockayne that he had admitted an 18 year old girl with pseudo-xanthoma elasticum. "That will be Vera Green," he said, and of course it was. He was intrigued by my own pedigree, because I had an English name but a Scottish home. "Poltallock, Argyll?" he said, "Ah, yes, the white woodcock in the Natural History Museum." (It was shot and presented to the Museum by my grandfather.) No wonder I was fond of him and thought he had the best intellect on the staff at Great Ormond Street. But he *was* odd.'

I saw far more of my other chief. Donald Paterson was a Canadian who, armed with the vigour, confidence, and drive that were considered to be typical of the products of the New World, had come to this country when quite young. In no time he had established himself as the best known children's physician (no one then called himself a paediatrician), had written several books, and published plenty of papers—mostly pot-boilers, for he was no medical scientist. He ran a flourishing practice from his house in Devonshire Place, at a time when no other physician was able to make a living if confining his practice to children.

To the archaic atmosphere then pervading the medical wards at Great Ormond Street, DP brought a whirlwind of activity—stimulating without being inspiring, was Dermod MacCarthy's not unfair description. His ward sister, Sister Manley, had perfectly adapted herself to DP's highly individual style and tempo—*allegro molto con brio*. She would explain to the new house physician how long experience had taught her how to manage this man, 'and if you do what *I* know he wants, we shall all get along'. I was well content to fall in with this pragmatic policy. However, the fact that my appointment had manifestly been made by the unmentionable Dr Cockayne started me off on the wrong foot. I was dreadfully inexperienced and my deficiencies were relentlessly exposed and commented on by a tyrannical DP. After three weeks I resolved to tender my resignation, on the grounds that my work was always going to dissatisfy him. I tackled DP to this effect before the next ward round. To my great surprise he denied any such dissatisfaction, and spoke warm words of encouragement. From that time on we got on well, and I profited much from his large clinical experience.

The resident staff totalled seven, with two house physicians, two house surgeons, a resident surgical officer, a casualty officer, and an anaesthetist. This last was a women, the first ever appointed (apart from the exceptional days of 1914–18). There was a medical registrar (George Newns) who was non-resident. His job rather surprisingly included doing all the postmortems. George Newns was available for help and advice during the day, but during the night hours when, as all know, most of the emergencies and crises happen, there was no one the house physician could turn to. It would have been unheard of to bother one of the chiefs. So the resident surgical officer (David Waterson), when not engaged in the theatre as was usually the case, was the one experienced person in the hospital. He it was who saw me through my first emergency tracheotomy.

The hospital was then in the course of rebuilding. Cocky's ward was still in the old building in Great Ormond Street, while DP's ward was temporarily housed in the top floor of the new nurses home in Guilford Street. (The latter arrangement made it tempting for a houseman to add interest to his late night ward round in the form of an occasional clandestine assignation.) The two wards were far apart—five minutes at a fast run—and inevitably a crisis in one of the wards would find me in the other.

There was a brisk turnover of cases in DP's ward, a good number of the children having been seen by him privately. It was sometimes hard to keep up, and a mongol (sorry, Down's syndrome) or other retarded child was warmly welcomed, as it blocked a cot for a week or two while being 'investigated'. This would probably include a request for Dr Wyllie's opinion. Dr Wyllie was in the unfortunate position of having the reputation of an interest in neurology; this he tried strenuously to play down, claiming that the only children he was ever asked to see were those with mental defect. Arriving to see such a case in the ward, he would approach with a resigned air, draw from his case an ophthalmoscope of the simple type sold to students, make a few perfunctory shots at scanning the child's fundi, and the visit was complete. A ritual performance? Yes, but in those days when medical knowledge was relatively scanty, much that passed for medical practice was largely ritual.

Asthma was then as now a common disease. DP sent these children in to be dealt with on a routine plan. Each child had an x ray of chest and antra (the latter often leading to an antral washout), a blood count, and sedimentation rate. Frenetic activity on the part of Sister Manley was required to ensure that all these had been done and the results to hand by the time of DP's next visit. The child was then sent home or to a spell of convalescence at Tadworth, to receive a course of injections of Bencard's Mixed Inhalants.

For the really severe asthmatic we had one sovereign remedy, to send the child to Davos in Switzerland for a period of months or years. The Davos scheme continued for many years, and required a paediatrician to make occasional visits. For a long time this not very exacting duty was happily undertaken by Richard Dobbs, whose visits were carefully timed to coincide with the most favourable ski conditions.

Gastroenteritis played a large part in our life; many acute cases were admitted, while cross infection within the ward was a continual worry. It was all too common for a well baby to come in for some minor procedure such as a hernia operation, only to go out in a coffin. Treatment usually involved an intravenous drip, which meant a cut down at the ankle, a houseman's reputation depending much on his expertise at this procedure. I gradually improved but never relished the tricky job of getting a cannula (Bateman's needle) into a minute vein, under the dim light of a torch held by a nurse. The only intravenous solution was normal saline (no potassium) infused in somewhat arbitrary amounts.

Meningitis was not only common, but often seen at a late stage when a meningococcal infection had become chronic ('post-basal meningitis') with the pathetic picture of a grossly wasted baby in extreme opisthotonos. Sulphonamides were just coming into use, but Prontosil, an intense red dye, was the only soluble form. I have memories of wrestling with a desperately ill baby at some ungodly hour of the night, one hand holding a needle inserted into the baby's cisterna magna and the other holding the infusion of Prontosil connected to the needle.

This was an era when the idea of focal sepsis was popular, and an adult with rheumatoid arthritis was likely to suffer a dental clearance. Analogously in the paediatric field, enteral disease was considered often a symptom of infection elsewhere in the body—'parenteral infection'. Cryptic infection in the middle ear was held to be particularly important in this context, and when in doubt it was thought wise to incise the ear drum. It was not unusual for the houseman to perform the myringotomy in the ward, having first himself anaesthetised the child with ethyl chloride given by mask. I had just completed the myringotomy in this way on one young child with an intractable diarrhoea, when the nurse said quietly, 'I think he's dead'. She was right. I was overcome by misery, knowing that my actions had been impetuous, incompetent, and probably unnecessary. The fact that I received sympathy from my seniors rather than the censure I felt I deserved mortified me. At the coroner's inquest, held in a courtroom in Marylebone I had to listen to the unctuous tones of the coroner as he assured the bereaved parents that the doctor concerned had selflessly laboured and used all his admirable skills in a fight to save their child's life. The proceedings ended with the clerk to the court handing me my fee as a witness: two guineas As custom demanded I pocketed the two pound notes and handed back to him the two shillings. I walked back to the hospital and there discovered that I did not have the two pound notes; I must have thrown them away in my utter disgust.

DP's famous 'circus' on Friday afternoons was an enjoyable feature of the week, when cases were demonstrated to any who cared to come. DP, something of a showman himself, liked his staff to show a case with some panache. Sometimes an expert was invited to speak, and in this way I met some of the medical celebrities of the time.

Less enjoyable was the weekly whooping cough clinic which fell to my lot to run. Whatever its original aim can have been, its purpose was now totally obscure. The scene was a sort of Dickensian version of Dante's Inferno, with a roomful of coughing, spluttering, whooping children supported by weary, distraught mothers. My regular assistant on these occasions was a porter of exceptionally lugubrious mien, who, armed with a mop and a bucket of sawdust, impassively dealt with the pools of vomit. Diagnostic tests included a leucocyte count, from which I at least learnt that a sky-high lymphocyte count—my record was 200 000—does not always mean leukaemia

Two recent publications had claimed that large doses of vitamin C curtailed the symptoms of pertussis. The clinic provided an opportunity to set up a controlled trial (the placebo was a spoonful of cod liver oil and malt); vitamin C was shown to be without effect. DP, a keen advocate of the publish-or-be-damned theory, persuaded me to write up for the *BMJ* this non-world shaking finding.

The other pair of medical firms at Great Ormond Street were those of Dr Frew and Dr Pearson, for whom I also did a stint as locum house physician. Dr Pearson was absent for long periods for health reasons, so his influence was slight. Dr Frew was chiefly remarkable for his skill in avoiding ever committing himself to any definite opinion about any of the children he was shown on his ward round. He was nearing retirement and was rumoured to be writing a textbook on the diseases of children. This seemed unlikely, but to everyone's surprise the book did appear. Surprise turned to shocked horror when readers discovered that according to the senior physician at Great Ormond Street, almost every disorder from enuresis to encephalitis was the result of a hitherto undescribed lesion—hyperphlebaemia, or overfilling of the veins. Strangely, that word had never been heard on the author's lips during the long years he had attended the hospital.

Besides the four physicians 'with beds' there were the outpatient physicians, W G Wyllie, Bernard Schlesinger, Wilfrid Sheldon, Reginald Lightwood, and Alan Moncrieff, from whom were to come many of the leading men among the postwar generation of paediatricians. From their outpatient clinics would arrive on the wards children labelled 'For admission this day', with a provisional diagnosis attached. The latter, with the irreverence of youth we were apt to demolish out of hand. Reggie Lightwood was famed for the vagueness of his diagnoses, one of which ran:? vomiting,? '?'.

The surgical side of the hospital was active and flourishing at this time, with a team of bright young surgeons, of whom the acknowledged star was Denis Browne (the only surgeon in London who confined his work to children). He was a man brimful of original ideas, and with the necessary drive to implement them. His cleft palate results bettered those of the plastic surgeons, and his contributions to orthopaedics, notably talipes, were becoming accepted internationally. We always tried to steer our pyloric stenosis babies to him for operation, which he did under local anaesthesia with an ease, delicacy, and speed which was wonderful to watch. He was said to have done over a thousand Ramstedts. 'Pylorics' were then usually diagnosed very late, and these babies came in wasted, dehydrated, and alkalotic, so ether anaesthesia, used by the other surgeons, was liable to be the last straw for them.

Nursing was of a very high standard, as a nurse could only start her children's training after becoming a state registered nurse. I was often painfully conscious of the disparity between my own experience and that of the nurses I was working with. Then as now there were never enough nurses, and the ward sisters seemed to be chronically at war with 'the office' where Matron was supposed to have any number of nurses, wilfully refusing to send out any of them to 'special' some particularly dire case.

The prevailing attitude to mothers is epitomised in the immortal words appearing in Sir Robert Hutchison's *Lectures on Diseases of Children,* '. . . these are apt to be loquacious persons, but it is always worth while to listen patiently to all they have to say. . .'. Visiting was limited to Sunday afternoons, and was discouraged altogether for the toddlers because they would be 'upset' by seeing their mother. I do not remember that any facilities were made available to enable a mother to breast feed her baby. But DP was unique in regularly setting aside time at the end of his ward round to see the parents.

Looking back on my time at Great Ormond Street half a century ago, I recall the sheer enjoyment and exhilaration of working there, but also the periods of overwhelming exhaustion. In part this was due to the work of looking after more than 50 sick children and the lack of sleep, but also to the excessive clinical responsibility that I as a house physician was landed with. Time off was virtually confined to alternate weekends. On one of these I reached home at teatime on the Saturday, fell into bed, and surfaced again next afternoon 22 hours later, just in time to set off back to the hospital.

A particularly sapping part of the job was the system by which I would be woken by a porter early in the morning with a message that Mr and Mrs Brown were waiting to be seen at the porter's lodge. Gradually it would dawn that Baby Brown, whom I had been up with the last few nights, must have died. Bleary eyed, half asleep, and irrationally resentful, I had to interview the stricken parents and, before signing the death certificate, ask their permission for a postmortem. It was all too much.

But a great deal was about to change, and in 1938 the number of house physicians was doubled to four, one for each ward. Two new posts were established with the somewhat portentous title of resident medical assistant and clinical pathologist, and these were filled by Ronald Illingworth and Elaine Field ('Another woman? What's the place coming to!'). More important still, a resident assistant physician was appointed (Dick Bonham-Carter), counterpart to the resident surgical officer, so at last a house physician would have someone at hand to consult.

There must be many people who, though greatly devoted to their parents, yet look back on their childhood and realise that their upbringing had been far from ideal. So the upbringing I received from my alma mater, Great Ormond Street, may have been less than ideal, but somehow it left me with a deep and abiding affection for the place.

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Queuing for admission to the outpatient department at Great Ormond Street in the 1930s.

Archives of Disease in Childhood, 1988, **63,** 1276–1280

Current topic

Much data but limited information in the NHS

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The report *Where are the children?* used routinely gathered NHS data from 1984 to determine where children admitted to hospital were being cared for and whether Department of Health and Social Security (DHSS) guidelines of some years standing were being followed.[1] These were the best data available nationally but the study showed several major defects.

Defects in data gathering

Although the regions were generally able to provide data on specialities admitting children, problems occurred in the following areas:

(1) CONFUSION IN IDENTIFICATION OF SPECIALITY CARE

Newborn babies receiving 'transitional care' may not have been identified and this may be one reason for variability in admission rates to special care baby units. Babies who have undergone surgery may be discharged from these units as a 'newborn' rather than a 'surgical case' and not be credited to that speciality. In older children, especially in childrens' hospitals, children receiving care from a paediatric surgeon may be recorded simply as a general surgical or urological case to the obvious disadvantage of the speciality of paediatric surgery.

Difficulties arose in comparing districts when treatment of children with infectious disease differed: their care being undertaken by either paediatricians or infectious disease consultants.

In intensive care units where a 'discharge or death' only is recorded, children may be undercounted because children were identified only when a death occurred: children transferred back to the children's ward were not recorded and, of course, children are rarely discharged home from an intensive care unit.

No data were available on children attending outpatients or, except for a few districts, accident and emergency departments, nor for those attending diagnostic or therapeutic departments.

(2) ADMINISTRATIVE DATA INADEQUACIES

In several regions definitions or identification of wards dealing with children were inadequate with obvious implications for nurse staff establishment and facilities for parents Indeed it was of concern to find that no information was available from districts on the numbers or location of registered sick children's nurses.

(3) DAY CASE OR WARD ATTENDER?

Day case admissions of children pose a particular area of difficulty. Most childrens' wards experience a considerable 'unlogged' workload from ward attenders, which often amounts to a further 20% of their recorded inpatient numbers.[2] There appears to have been wide variation in the recording or definition of these cases.

Children in hospital

Despite these defects a broad picture of care of children in hospital in 1984 became apparent.

WHERE WERE THEY?

There were 878 553 child inpatients (age 0 to 16), which represents 16% of all hospital admissions of all ages to all NHS hospitals in 1984. Of these children, a half were under 5 and a third under 2 years of age. Although some of these will be readmissions of the same child, some idea of the scale of demand upon inpatient facilities can be obtained by stating that these figures would represent between 7 and 10% of the total population aged 0 to 16 or for the age range 0 to 4 years, 11 to 18% of the population of that age group in England in 1984.

About one in four children discharged still appear to be from an adult or mixed ward.

Most regions admit between a third and a half of adolescents with medical conditions under the care of general (adult) physicians, nearly all of these teenagers being treated on adult wards

WHO CARED FOR THEM?

Paediatric medical staff were directly involved in 43% of these child admissions in addition to their care of normal newborn babies. The remaining 57% of child admissions were under the care of surgical specialties when paediatric medical staff are often involved assisting in the care of small babies. Nursing staff always are involved of course. There has been an increase in the number of admissions to hospital over the period 1974 to 1984, especially in the younger age groups, despite the (slow) growth in the use of day care. There is also reason to believe that day cases have been significantly undercounted.[2] These changes have major implications for the nurse staffing establishments of childrens' wards and for the provision for parents and families.

New data and information systems

The defective data collection will come as no surprise to clinicians all of whom are probably aware of the considerable energy and expense directed to the improvement of NHS information in the form of the development of performance indicators and from April 1987, the introduction of the recommendations of the Körner report.[3] It seems timely to examine what is happening to see whether the changes will be of help to paediatricians who perhaps more than other specialists are used to reviewing NHS statistics relevant to their work.

Performance indicators

'Performance indicators are designed to inform judgements about how well NHS services are being provided'.[4] The first package of performance indicators[5] provoked a mixed response[6] and while some of those available were of interest others were of little value. 'Tracer conditions' were selected in a rather odd way or were based on insufficiently precise diagnostic data. It is already possible, however, to obtain a display of the workload of a paediatric unit related to population served (catchment or resident) and of the bed number, clinics, and staffing resource to meet these demands (although the medical manpower data on which this information was based were incorrect). Some clinicians are not aware that their district will have this information on computer disc from the John Yates district profiles[7] and the DHSS performance indicators package.[8]

The display allows comparison with other units in the region or nationally in the form of a histogram. Future refinements of these data should allow provision for children to be measured against a minimum standard which could be set (but by whom?) so that those districts falling far below this could make strong cases of need for the problem to be rectified. Attempts to examine certain data such as length of stay or admission rates for specific conditions—'tracer conditions', for example, asthma—may allow comparisons between districts. The purpose to which this comparison is to be put is still questionable, however, and although it may highlight local problems and in this way prove useful (for example, social adversity or differing clinical practices), it is essential that the data are analysed by managers and clinicians working together. It is also essential that the diagnoses chosen for these 'tracer conditions' are such that districts will be comparing like with like (somewhat unlikely until the input of diagnostic codes is improved considerably).[9] The information that comes out, of course, is only as good as that put in. Clinicians have a major responsibility here to assist those recording these data with the use of codes from the International Classification of Diseases including sometimes the use of the fifth digit necessary, but rarely used, in a number of paediatric conditions.

The new performance indicators proposed in 1987[4] attempt to build upon the experience of the use of the first DHSS package and of John Yates district profiles.[7] Consultation has taken place but it remains to be seen whether it will be necessary to await the next but one package before adjustments are made in the light of the comments received by the DHSS.[10]

There are already some evident difficulties. Emphasis is given to basing the workload in a district on the resident population or catchment population as perceived by a health authority. While this will work in most areas it is not appropriate in inner cities or in regional centres providing a tertiary referral service. Indicators should be interpreted in the context of the nature of the population served and these data are available based on data from the Office of Population, Censuses and Surveys from the John Yates district profiles on computer disc for each district in the form of a 'Jarman' index (which includes information on numbers of children under 5, one parent families, immigrants, and the unemployed, etc).[11] Some consideration should be given to showing the *type* of work done in a department in future. The neonatal data need to be improved to identify neonatally trained nurses for example, or numbers of babies treated after transfer in utero. Some of the data being collected in the community will be of no value unless what is being collected is defined much more precisely—for example, when schoolchildren being examined are counted it is not made clear who is examining them: nurse or doctor. Hopefully after recent events, the original lack of intent to count nurses who are trained to work with children, for national comparison, will be rectified.

Körner reports

The systems recommended by the Steering Group on Health Service Information (Körner reports) make an avowed start on the improvement on NHS information.[3 12] Patient information systems are used which replace the statistics of SH3, hospital activity analysis (HAA), and hospital inpatient enquiry (HIPE) and provide minimum data sets aimed principally to provide:

'. . . information for the health services management. Thus we have not tackled specifically the information needed by health professionals to evaluate the results of their care; nor that needed by individual professional bodies to review the resources available to aid the professional work of their members' (paragraph 2.7, First report).[3] Maternity services are excepted from this however, as there is an intention to assist clinicians 'in reviewing the process of their care'. Nevertheless, paediatricians should attempt profitably to use the data that are held combining this with the data from performance indicators to obtain a picture of their practice from the managers' viewpoint.

A major drawback of the Körner reports are that 'outcome measures' (the result of therapies) are not fully considered and there is a need to extend the dialogue with the professions to determine what these should be. It appears though that it could be some years before these would be credible in view of the inaccuracy of the diagnostic data held in the past.

Inpatients

The minimum data set which includes the diagnosis is to be collected on all inpatients and day cases. Ward attenders would only have this information collected if a decision is made to do so locally, which paediatricians could influence. Clinicians should note the new proposals relating to inpatient activity. Bed occupancy is no longer regarded as an appropriate indicator of efficiency of bed usage (paragraph 9.38, First report).[3]

'From basic data such as the number of bed days intended to be used, actually available and used, and the number of patients treated, statistics can be derived which serve as indicators of the effective use of beds. However, the cessation of data collection about specialty bed availability means that traditional statistics which incorporate this measure such as specialty bed occupancy, specialty turnover interval and specialty throughput per available bed can no longer be calculated in the same way.'

Now a 'ward inventory' will need to identify those beds in aggregate for use by children as a patient group within the district and paediatricians, exercising their role of overall supervision of childrens' services, together with the nurse managers should ensure this is correctly done. The availability of such beds can be analysed daily. Utilisation of these beds by differing specialties will be analysed in the form of *length of stay* and *throughput per available bed* (paragraph 9.41, First report).[3] Such analysis will require that each specialty within a district have a nominal allocation of beds by management which are intended for its use. Each district will have to send to the region its intended use of beds for each specialty (paragraph 9.43, First report).[3] Some of the beds allocated to each of the surgical specialties treating children and all the beds used by the specialty of paediatrics will be on a children's ward. This change will be especially important for those districts which have up to now used the childrens' wards on a very flexible basis and clinicians should be involved in the allocation. Under the new arrangements, when a bed is 'borrowed'—for example, if a paediatric patient occupies one of the beds allocated for surgical use on a children's ward—then the paediatric bed number is increased and the surgical number decreased for that day. Subsequently, the 'throughput per bed' will be calculated over the period using the additional bed number.

This change should provide a clearer picture of workload and should show inappropriate bed allocation. For example, an unusually high throughput per bed for paediatrics could indicate (a) an inadequate number of beds for the catchment population; or (b) be explained on the basis of an exceptionally high population of children in the population served; or (c) a popular subspecialty interest in the district; or (d) relatively deficient primary care or a deprived community in an inner city; or (e) an unusual case mix such as admission of head injuries under a paediatrician's care.

Information from the data will be routinely available and separately upon both the activity of the ward and upon each specialty: and if necessary, each day's activity can be examined to illustrate the fluctuations in usage. The summary will also show usage in terms of bed days and it will be easier to examine the relative use of childrens beds by specialty.

Clinicians will need to become familiar with these new systems of display of their work.

Outpatients

The recording of data on outpatients in surgical specialties will allow local analysis of the attendances of different age groups and show the childrens' workload being dealt with This must prove an advance for the planning of facilities for children. Also numbers of children attending therapeutic departments can be obtained but not regrettably the number of children attending diagnostic departments (pathology or *x* ray). It is a pity that diagnostic data are not to be collected yet on outpatients.

Community

There will be an increase in the data collected in the community but further experience needs to occur before it is clear whether this will be helpful to clinicians in child health practice.

Day cases/ward attenders

Part of the development over the years in paediatric practice has been an increase in ward attenders' work (although the scale of the increase has not been possible to measure as they have not been recorded). If a child attends under a regular arrangement to the ward then he could be regarded as an outpatient but this is unusual and most such patients will have been recorded (if at all) as a day case or even less likely, a ward attender. Under the Korner report recommendations this should improve (ward attenders will at least be counted) but only if the definitions are not regarded too rigidly: for example, a child who properly should be regarded as a day case because of the treatment received but who spends less than the defined 'few hours' on the ward or who does not use a bed could incorrectly be counted as a 'ward attender' on whom the collection of diagnostic data or a minimum data set is optional. Indeed it is highly desirable that the minimum data set is collected on ward attenders as it is on day cases,[2] and clinicians should press for this to be done in their districts. The pattern of care provided in this way is in the interests of children and units should not be ' .. penalised through failure to capture data about them' (paragraph 3.11, First report),[3] as Körner has recognised. Such data collection is the first step in getting adequate staffing to meet this workload!

Neonatal practice

Under the recommendations of the Körner report newborn babies are recognised as a specific patient group and indeed the type of care received (normal, special, or intensive) will be recorded. The minimum data sets, however, will incorporate the expanded information, endorsed by the British Paediatric Association (paragraph 6.14, First report)[3] only as a local option which should therefore be pressed for. It may be necessary to point out that the admission of a newborn differs from a paediatric admission and its activity must be analysed separately and that each maternity bed does not have an associated neonatal cot (some are antenatal beds).

Comment

In order that the data derived from the Körner report or performance indicators are to be valuable in child health practice, it is essential that its limitations are known to clinicians and to managers. It may be a faint hope that too much decision making is not to be based on the presently available data until their accuracy and completeness have been substantially improved. The information needs also to be interpreted in the light of local circumstances rather than be used to provide managers with a goad to provoke greater effort from already pressed clinicians or worse, as a reason for removing resources from a service which superficially appears to be overprovided or underused. In some instances hopefully, the data will be of help in obtaining greater resource but again only if interpreted in the light of their limitations and local conditions.

Managers must understand the nature of paediatric practice—that is, practice which is largely responsive to uncontrolled demand that fluctuates over the week or year—and clinicians should be prepared to help them to do so. Also that while older children especially are treated at home, there is an increase in the admissions of babies to hospital (with increased needs for nursing staff and for doctors skilled in their care). Consequently while a children's bed in the district may be empty a *suitable* bed (for example, a cot and cubicle for a small baby) may not be available. Also when childrens' wards are full, children cannot be slept out on an adult ward. Thus it is necessary and desirable to have unoccupied beds to retain flexibility even though on 'performance' this is likely to be regarded as a bad thing.[3] Similarly, relatively high numbers of return visits to outpatients or as ward attenders may represent good practice in supporting primary care of such chronic conditions as epilepsy or in treating acute or complex illnesses at home.

Buried in non-paediatric statistics are measures of workload provided for children, and managers may need to be guided to recognise this by the display of inpatient and outpatient data in the age bands 0 to 16 years or in smaller bands.

It seems inevitable that 'performance' will continue to be evaluated in some way from henceforth for a variety of purposes. Paediatricians should ensure that some of these purposes are their own. There seems, for instance, little doubt that centralisation of all childrens' services on one site will lead to the most effective use of resource—the manager's first priority—and the best service for children and their families—the paediatricians'.

The new arrangements for analysis of work patterns does, however, place considerable responsibility upon clinicians to ensure that the system will operate in the best interests of their service and the children they serve.

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Personal practice

Establishing breast feeding in hospital

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SUMMARY The experience and practice of the author is described in her appointment as a breast feeding advisor to the paediatric and obstetric units at University College Hospital with special responsibility for supervising infant feeding, especially breast feeding in the maternity unit. During 1980–5 there were 13 185 mothers whose babies fed. The feeding method of 12 842 mothers was recorded on discharge from the postnatal wards and 77% were breast feeding; only 3% of these mothers gave complement feeds of infant formula. The practices in the maternity wards to enable mothers to establish successful breast feeding and the methods of dealing with common problems of breast feeding are described.

Breast feeding has undoubted nutritional advantages. The composition of human milk cannot be bettered by manufactured artificial feeds. It also helps to protect the infant from infections by passing on immunoglobulins, the iron binding protein lactoferrin, living cells, other bacteriostatic and antiviral factors from the mother. It may have a role in reducing allergies in fully breast fed infants. Successful breast feeding is immensely satisfying to both mothers and babies, and the emotional benefits cannot be ignored. It is a long standing government health policy to encourage all healthy mothers to breast feed their babies.[1–3]

The incidence of breast feeding in England and Wales was 51% in 1975,[4] 67% in 1980,[5] and 65% in 1985.[3] (Incidence of breast feeding is defined as the proportion of babies put to the breast even if on one occasion only.) Half in 1975 and one third in 1980 and 1985, however, had stopped breast feeding by the age of 6 weeks. Many mothers who would like to breast feed either never get started properly or stop very quickly (12% in one week, and 37% by six weeks).[5] Almost 50% of 'breast feeding' mothers had given bottles of infant formula by the time they left hospital and so did not establish full breast feeding. Breast feeding rates in the United Kingdom are higher in social classes I and II, first babies, and in mothers educated beyond the age of 18 years. Events around the time of birth—for example, caesarean section and postnatal ward practices—also influence it.[4 5]

University College Hospital unit

The University College Hospital unit is a teaching hospital obstetric unit (but not a midwifery training school) so that obstetric cases are referred to it for specialist care. It includes the North East Thames regional neonatal unit. Locally it serves an inner city area with complex social and housing problems. The population is multiethnic and a large proportion do not speak English. Until 1986 there were about 2000 deliveries a year, but after reorganisation there are now over 3000.

Between 1980–5 the method of feeding by 13 185 mothers was recorded on discharge from the postnatal wards at the hospital. A total of 343 (3%) mothers were excluded as their method of feeding was unknown. The breast feeding rates of 12 842 mothers whose method of feeding was known between 1980–5 is shown in the table.

During 1980–5 out of a total of 10 597 mothers, 1676 (16%) had a caesarean section; of these 1309 (78%) were breast feeding on discharge. (The 1981 figures were not available.) The usual length of stay in hospital after a vaginal delivery was seven days for primiparas, 48 hours to seven days for multiparas, and 10–14 days after caesarean section. In 1986

Table *Population of the University College Hospital maternity unit and breast feeding rates (1980–5)*

	No (%) from each population group	*No (%) who were breast feeding on discharge*
Total mothers	12 842 (100)	9956 (77)
Ethnic origin:		
White/European	10 524 (82)	8023 (76)
Afro-Caribbean	723 (6)	654 (90)
Indian/Pakistani/Bangladeshi	797 (6)	624 (78)
Chinese/Japanese	118 (1)	86 (73)
Other	680 (5)	569 (84)
Social class (n=10 566*)		
I, II, III non-manual	5450 (52)	4662 (86)
III manual, IV, V	3679 (35)	2467 (67)

*Social class figures for 1983 unavailable

there was a change towards earlier discharge for all mothers. A total 1104 (9% of 12 842) babies had a birth weight of 2500 g or less

Antenatal support for infant feeding

Only 33% of women have decided how to feed their baby by the time they become pregnant.[4] At University College Hospital the mothers who attend classes on infant feeding tend to be those who have decided to breast feed. The antenatal class covers the practical aspects of how to breast feed, what problems may arise, who will help, advice on appropriate family diet, smoking, alcohol, contraception, and the basics of bottle feeding and weaning. All mothers are given the author's practical written notes 'How to feed your baby' (also translated into Bengali) at the 28 week antenatal visit or at the class and in the postnatal wards. Methods of encouraging breast feeding among those who do not attend classes need to be found and evaluated.[3]

Many women are not ready psychologically to absorb much information about the care of the baby until movements are felt or the baby is seen on an ultrasound scan. Once the baby is born feeding becomes the focus of concern! Postnatal care concerned with establishing breast feeding is of paramount importance to mothers and this time in the ward provides a marvellous opportunity for health education and emotional support.

Before discharge from the postnatal ward, the sister from children's outpatient department visits each mother to give her the telephone number of the children's outpatient clinic and any follow up appointment. The community midwife is informed by telephone of each mother and baby's discharge, the mother is given a discharge letter to the community midwife, an obstetric summary is sent to her general practitioner, and the method of feeding recorded.

Sound breast feeding practice

Can all mothers breast feed? Most mothers can breast feed. At some periods 96% of mothers of social class I and 95% of African mothers were breast feeding on leaving the hospital. Antenatal examination of the breast is important to exclude any pathology. It also allows a woman to voice any anxieties she may have about her breasts and to discuss feeding her baby. Inverted nipples can cause difficulties in latching the baby to the breast but I do not advise Waller shells; they cause oedema of the areola, and there is no evidence that they aid protractility, which usually improves towards the end of pregnancy. It is very rare indeed for a skilled midwife to be unable to fix a baby soon after delivery, when the breast is still soft. Many women who have had breast surgery can still breast feed. Any mother who wishes to breast feed should be allowed to try.

Can all babies be breast fed? Any baby who can suck can be breast fed and milk can be expressed for those who cannot. Colostrum varies in amounts from a few drops to 45–50 ml or more and a mother will produce milk, however prematurely her baby is born. Poor sucking should always alert staff to the possibility of hypoglycaemia or hypothermia, prematurity, or hypotonia so that paediatric advice is sought At University College Hospital many babies of 34–36 weeks' gestation are cared for by their mothers in the postnatal ward so that they can breast feed more easily. Twins can be breast fed. Offering one breast each ensures that both babies get their fair share of fore milk (containing more water and protein) and hind milk (containing more fat) If a mother is short of milk, she breast feeds one baby at one feed and the other one next feed and alternates breast and bottle for each baby.

Mothers are more likely to produce enough milk if they breast feed on demand in the initial stages. A hungry baby has an active rooting reflex which is lost when the baby has fed enough. In practice, if a baby has fed on delivery, another feed may not be needed for up to six hours. Thereafter, most babies feed at intervals of two to four hours, but often increase the frequency to 10–12 feeds on the 3rd or 4th day for 24 hours. But as the milk comes in and the baby begins to regain his birth weight, the feeds space out to intervals of three to four hours. The frequent feeding period is a physiological response of the baby to the initial average 5% weight loss and ensures that the mother makes enough milk for her baby's individual needs. A mother and the staff need to know this, because complement infant formula feeds are often offered in the mistaken belief that there is insufficient milk.

How long should a baby suck? There is great variability in sucking times, and little benefit in timing sucking. Babies on the breast suck in bursts of sucking with light 'flutter' sucking followed by long swallowing sucks as the baby gets milk, and then pause. The light sucks seem to evoke the milk flow reflex, which is a conditioned response to the baby's cry for a feed or to warming of the nipple in the baby's mouth or in a warm bath.

To encourage breast feeding, babies should be beside the mother and should be breast fed by the mother at night as well as during the day. Breast fed babies should not be given artificial feeds in the night. Every milking or suckling stimulus causes a rise in plasma prolactin necessary for the initiation and maintainence of breast feeding [6]

If a baby is hungry, frequent feeds will stimulate the breast to produce more milk, whereas unnecessary complement feeds will inhibit this. Night feeds will be demanded for six to 10 weeks depending on the size of the baby, and nothing is to be gained by offering drinks of water instead.

The first feeds

The first feeds are of vital importance for the initiation of lactation and should be started on delivery or within the first four hours of birth. Delays of 24 hours make a good supply of milk less likely.[4] With help mothers who have undergone a caesarean section can breast feed immediately after delivery. I find that shortage of milk in later lactation or damage to the nipples can often be traced back to problems with the first feeds. Conversely, if a baby has fed well at this stage, it is a virtual guarantee that the mother will produce enough milk, and that even if she has difficulties later with full breasts or an unwell baby, she will be able to continue breast feeding.

Latching babies to the breast

Learning to feed involves calling up a reflex response and initiating a change of behaviour evoked by a pattern of stimuli—for example, the shape of the nipple and areola. It is the feel of the nipple against the palate which makes the baby suck. 'Subsequent reinforcement leads to increased eagerness of the baby when put to the breast once it has had that experience. If the shape of the breast makes this difficult, the successful taking of the breast waits on skilled positioning so that the nipple goes further into the baby's mouth.'[7]

Damage to the nipples is prevented by latching the baby to the breast properly. The chin must drive into the breast to enable the nipple to reach the palate, so the baby needs to put its head back and up. 'If the baby's head becomes too flexed, the nipple touches the lower jaw and tongue and the nose gets too close to the breast. Helping the chin to thrust forward and the head to tilt back is hindered by pressure on the back of the head but helped by supporting the baby's back at shoulder level, with the baby facing the mother, chest to chest.'[7] Failing to position the baby correctly damages the nipple, causing a stripe of bruising across it.

Colostrum provides all the nutrients and water that a term baby needs, and has large amounts of secretory IgA in it. The practice of saying 'that the milk doesn't come in until the fourth day' is to be deprecated. It reinforces a mother's feeling that there is nothing there, and leads to offering complements or supplements of water, dextrose water, or infant formula feeds, all of which are entirely unnecessary for a healthy infant.

Complement feeds of infant formula

The practice of giving infant formula feeds to breast fed babies at night should cease. In the 1980 survey of the office of Population, Censuses and Surveys (OPCS), 50% of breast fed babies received complement feeds.[5] My experience is that they are very rarely needed by term babies. Complement feeds of infant formula interfere with breast feeding by: (a) reducing suckling, prolactin secretion, and the milk supply, (b) reducing suckling, oxytocin secretion, and the release of milk; (c) undermining a mother's confidence in her ability to produce milk; (d) possibly sensitising the infant to cows' milk protein; (e) altering the infant's gut flora· and (f) teaching a baby bottle sucking rather than breast sucking technique.

Weaning from the breast

Many mothers enjoy breast feeding their babies into the second year, and provided that weaning foods are introduced from 4 to 6 months, they can continue to breast feed as long as they wish. Particular attention needs to be given to some Asian mothers, to ensure that appropriate foods are introduced at 4 to 6 months because it is common for breast feeding to continue until 2 years of age without supplements of weaning foods. Vitamins A, D, and C may be needed by both mothers and babies. Weaning from the breast should always be a gradual process, a feed at a time to avoid leaving the breast overfull, when mastitis is more likely to develop. A bottle or cup is given instead.

Common breast feeding difficulties and their management

(1) DAMAGE TO NIPPLES

Every doctor, midwife, and health visitor looking after mothers and babies should be able to deal with the common problems of breast feeding. Bruising or blistering of the nipple is always a consequence of misfit between the baby and areola, sometimes due to inexperienced positioning of the baby on the breast. Healing occurs by resting the nipple, expressing milk by electric pump, and the correct positioning of the baby. If milk is not expressed or the baby is given infant formula feeds instead, the breasts receive insufficient stimulation and the milk supply is jeopardised. A melolin dressing can be used to prevent the nipple becoming adherent to a breast pad. A fissure of the nipple occurring after the puerperium is often caused by thrush infection of the baby's mouth and the mother's nipple It is best treated with miconazole gel or nystatin application to both until four days after it appears to be clear.

(2) INSUFFICIENT MILK

The hungry baby is difficult to ignore. If a baby never settles after feeds, the baby is always crying, the feeds take a long time, with one feed running into the next, that means that the baby is hungry and needs more milk. Weigh the baby. Babies should gain 150 to 200 g per week for the first 3 months. A feed needs to be watched to see if the baby is properly on the breast and to assess the feeding situation. If 24 to 48 hours of frequent breast feeds do not increase the milk supply, the baby will need complement feeds of infant formula milk by bottle. A complement feed is one given after the breast and the baby should take as much properly mixed formula as it wants. Usually 10 minutes a side on the breast followed by the bottle is a satisfactory compromise for the mother who wishes to continue breast feeding. Any one of the modified infant formulas may be used as a complement feed in this situation and soy milk should only be used if there is proved milk allergy in the parents or siblings. Many babies exhibiting catch up growth—for example, 'small for gestational age babies'—are often particularly hungry, feed frequently, and take large feeds. If a mother (and her helper) realise this, she can cope with the situation and continue breast feeding.

(3) ENGORGEMENT OF THE BREAST

This is unusual when babies are breast fed on demand. There is flushing and tenderness of both breasts, and though there may be fever, in contrast to acute mastitis the axillary lymph glands will not be swollen. Engorgement seldom lasts more than a few hours and is relieved by the baby feeding. Expressing some milk (preferably with an electric pump) relieves the severe pain but care should be taken not to overdo it. The more milk that is taken off, the more the breast produces.

(4) ACUTE MASTITIS

Acute mastitis occurs more commonly if the nipple is damaged. After the puerperium it may be associated with leaving the breast overfull during weaning. Symptoms of influenza, pain in *one* breast with flushing and induration, and swollen axillary glands are diagnostic. A sample of expressed milk should be sent for culture and sensitivity. The most common organism is *Staphylococcus aureus,* often resistent to phenoxymethylpenicillin. Therefore flucloxacillin or erythromycin are suitable antibiotics and will not harm the baby. Treatment should be commenced immediately. *It is important that the baby should continue to feed from the affected breast first: to empty it.* Otherwise the infection may spread and an abscess form. Massage of the breast is contraindicated for fear of spreading the infection. If the milk supply is reduced complement feeds may be needed temporarily. But the supply usually increases again as the infection resolves. Recurrent mastitis is usually a result of inadequate treatment, with either the wrong antibiotic or too low a dose for too short a time. Treatment should continue for a week. The baby may be a staphylococcus carrier and need treatment.

(5) BREAST ABSCESS

A breast abscess may result from neglect or inappropriate treatment of acute mastitis in lactation. The signs of acute mastitis are present, except that there is fluctuation of the indurated area Surgical incision and suppression of lactation with bromocryptine is indicated, though the baby may feed from the unaffected side to relieve discomfort until the milk supply is reduced

Importance of informed and consistent advice

Education of medical and midwifery staff is necessary to avoid the mistakes and misconceptions which so often result in conflicting advice. A postnatal maternity unit is absolutely dependent upon having sufficient experienced midwifery staff. Shortages lead to an immediate fall in breast feeding incidence, and a rise in breast feeding problems.

At University College Hospital a breast feeding clinic is held in the children's outpatient department so that babies can be weighed and paediatric advice sought. Appointments on a phone in basis are given on the same day if possible.

Breast feeding problems are urgent. Mothers refer themselves or are referred by the postnatal or paediatric staff, community midwife, health visitor, or general practitioner. Breast feeding consultations are time consuming because of the need to watch a feed through and this may be therapeutic in itself. The father of the baby is encouraged to be present. Parental relationships are often under stress and need support. The father can help the mother by feeding the baby in the night with expressed milk if the mother needs extra sleep. A mother may need her confidence built up, especially if she has had conflicting advice. At the same time a short note to the general practitioner or health visitor can help avoid this.

The pleasure of breast feeding her baby successfully is, for many women, one of life's most rewarding experiences. To enable women to overcome problems in doing so is one of mine.

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Special report

Vegetarian weaning

NUTRITION STANDING COMMITTEE OF THE BRITISH PAEDIATRIC ASSOCIATION

1 Introduction

1.1 BACKGROUND

1.1.1 The proportion of the British population following a vegetarian diet today may be larger than ever before. Immigration, particularly from the Indian subcontinent, has introduced to Britain many families who follow vegetarian diets for religious and cultural reasons. In addition widespread interest in conservation and environmental issues, concern about food additives, and attempts to achieve purpose in life through combinations of physical and spiritual disciplines have stimulated enthusiasms for vegetarianism among indigenous Britons.

1.1.2 With many vegetarian diets the provision of adequate nutrition for infants and children is not difficult. Some regimens may even have health benefits for older children and adults as they are usually high in fibre and low in cholesterol and saturated fatty acids. Traditional practices which include well established and successful dietary patterns provide guidance and support for families trying to achieve adequate and balanced diets on many of these vegetarian regimens. Otherwise some nutritional knowledge or dietetic advice is necessary to ensure adequate nutrition over the weaning period.

1.1.3 The whole population is at risk from diets which severely restrict the variety of foods eaten. Weanlings are, however, at particular risk because of the problems inherent in: (1) changing from fluid to mixed diet; (2) high nutrient needs for rapid growth; and (3) susceptibility to infection which itself may adversely affect nutrition.

Where mothers have been receiving nutritionally inadequate vegetarian diets, breast fed infants are likely to suffer the same nutritional deficiencies as their mothers, particularly vitamin and mineral deficiencies. By the age of 4 to 6 months (if not before) these deficiencies of intake may have reached critical levels. Thus the need for excellent nutrition at weaning may be even greater for the infants of vegetarian mothers than for the infants of those on normal mixed diets.

1.2 TERMS OF REFERENCE

The purpose of this paper is to outline vegetarian regimens and the hazards associated with them and to provide guidelines to the doctors and others concerned with advising on weaning diets for vegetarian children.

2 Terms of vegetarian diets

2.1 Vegetarian is not a specific term. It covers a wide variety of diets with very different restrictions,[1–3] but with partial or complete abstention from animal foods, eggs, and dairy products. Some vegetarian disciplines are outlined below.

2.2.1 SEMIVEGETARIANS

These eat some meat (for example, fish and chicken) but not red meat. Often the diet is followed for personal preference and varies between individuals.

2.2.2 LACTO-OVO VEGETARIANS

These eat no meat but eat dairy products and eggs Yogic vegetarians are lacto-ovo vegetarians who stress the importance of natural and unprocessed foods in the diet.

2.2.3 LACTOVEGETARIANS

These eat dairy products but neither eggs nor meat.

2.2.4 TOTAL VEGETARIANS

These eat no dairy products, no eggs, and no meat and thus consume no animal foods. Vegans are a group of total vegetarians who are not only united by dietary disciplines but by 'the desire to remember man's responsibilities to the earth and its resources and seek to bring about a healthy soil and plant kingdom and a proper use of the materials of the earth.'[4] Vegans accept the need for vitamin B_{12} and D supplements to their diets.

Fruitarians follow a total vegetarian diet but also exclude cereals and pulses as well as animal products.[5]

2.2.5 FOOD ADDITIVE AVOIDANCE

Those following diets which avoid food additives may pursue vegetarian diets in some form and in addition may concentrate on so called natural plant foods. The diets are often self prescribed and may be bizarre. When the natural food is raw unpasteurised cow, goat, or sheep milk, there is real risk of bacterial infection due to contamination of the milk.

3 Religious and cultural dietary restrictions leading to vegetarianism

There is great variety in the vigour with which followers adhere to religious and cultural dietary restrictions. The table outlines the restrictions affecting the diets of some groups.

3.1.1 JEWS

As avoiding pork, fish without fins, shellfish, and foods which have not been prepared by kosher methods are the only dietary exclusions, Jewish diets are neither vegetarian nor particularly likely to put weanlings at nutritional risk. Strict orthodox Jewish dietary practices, however, define foods which can, or cannot be, prepared and eaten together Meat and milk, for example, must be prepared separately and not eaten after one another unless several hours have elapsed. The extra labour involved in food preparation may impose stresses on the mothers of young children which, together with difficulty in some non-Jewish areas of obtaining kosher foods, could present problems for weanlings. Because of the difficulty ensuring that bought foods are correct, some Jewish families adopt lacto-ovo vegetarian diets.

3.1.2 HINDUS

Hindu dietary practices vary according to the branch of Hinduism followed and individual strictness of adherence. The practice of non-violence against living things means that some Hindus eat no animal meat or fish Strict Hindus do not eat eggs. Western cheese may also be forbidden as it contains animal rennet or gelatine. Other Hindus eat meat but traditionally avoid the meat of the cow (beef, veal, sausages, beef extracts) as the cow is a sacred animal, and of the pig because it is considered unclean. Milk and ghee are sacred foods and dairy products are an important part of the diet.

Jains are members of a non-Brahminical Hindu sect with dietary restrictions similar to those of Buddists. They are strict vegetarians and fast frequently as well. Many avoid 'hot' foods which include eggs, fish, tea, honey, brown sugar, lentils, carrots, onions as well as the foods most Europeans would regard as hot: ginger and chilli.

3.1.3 MUSLIMS

Again there is tremendous variety both in the rigidity of adherence to, and the interpretation of, rules by different sects. Pig meat and the blood of all animals must be avoided. Animals should be slaughtered after the 'halal' ritual. Fasting from sunrise to sunset occurs during the lunar month of Ramadan but young children do not usually fast.

3.1.4 SIKHS

Although Sikhs follow a separate religion, their dietary customs overlap with those of Hindus and Muslims. Some are vegetarians but many eat eggs and meat, although animals should be killed with

Table *Guide to foods avoided by certain religious practices*

	Pork	*Beef*	*Other meat*	*Non-scaly fish, shellfish*	*Eggs*	*Milk*	*Canned foods*
Religion:							
Jewish*	×			×			
Hindu*	×	×			?		
Jain	×	×	×		×		
Sikh*		×					
Muslim*	×						
Buddhist	×	×	×	×	×	?	
Bahai	?	?	?	?	?	?	
Seventh Day Adventist	×	×	×	×			
Rastafarian	×	×	×	×	×	?	×
Macrobiotic (Zen)	×	×	×	×	×	×	×
Hare Krishna	×	×	×	×	×		×

*Dietary restrictions may be greater if foods not prepared in acceptable way
×Foods generally avoided
?Denotes considerable variation within religion over consumption of these foods

one blow (khakka). Some eat pork but not beef. In practice their diet is largely meat free.

3.1.5 BUDDHISTS

Buddhists avoid killing any living thing. Strict Buddhists avoid eggs and milk.

3.1.6 The traditional diets of Hindus, Sikhs, Muslims, Buddhists, particularly for less strict adherents, can achieve nutritional adequacy for weanlings fairly easily.[6] Problems may arise when trying to provide an adequate diet for children in Britain due to difficulty in obtaining foods prepared according to religious laws and to uncertainty over whether food bought ready made or in jars or tins has been handled inappropriately or contains forbidden foods. Commercial infant foods which are recognised as correct may be limited to tinned fruits which are commonly of lower energy density then some of the savoury meals and cereal products.

Religious practices other than dietary restriction may influence nutrition. Eating in the home may be by hand and right hand only—not easy for small children. Fasting does not normally involve young children but a mother who is herself fasting may have little energy and interest in preparing meals for her young children. Where meals are traditionally only twice a day and one meal late at night, problems may also arise from the volume of food young children have to consume at each meal and because the children are too tired or too hungry to eat.

3.2. The religious practices described above have long traditions. Customs and recipes have developed to avoid some of the more likely nutritional deficiencies. Dietary practices developing in association with more recent religions and cults may not always have the same secure nutritional basis. The dietary regimens associated with some of these are outlined.

3.2.1 SEVENTH DAY ADVENTISTS

The moral importance of a meatless and stimulant free diet is part of the belief of this movement. Tea, coffee chocolate, and many food flavourings are not allowed. Milk is acceptable The first commercial breakfast cereals (cornflakes) evolved from the search for a tasty acceptable food which fulfilled the Adventists' dietary strictures.[7]

3.2.2 BAHAIS

Vegetarianism is not at present obligatory on Bahais although Bahai writings state that the diet of the future will be fruits and grains. Many Bahai do follow vegetarian (often total vegetarian) regimens now Fasting at specific times is obligatory on Bahais between the ages of 15 and 70, although pregnant and lactating women are exempt.

3.2.3 RASTAFARIANS

The advent of this movement in Britain is relatively recent but the concepts on which it is based date back to the 17th century.[8] The extent to which followers adhere to particular dietary practices varies. Orthodox Rastafarians avoid all animal products, eggs, alcohol, salt, and canned foods. Diets concentrate on chemical free, organic foods. Some Rastafarians drink milk.

Foods acceptable to strict Rastafarians are foods which are 'total' or in their natural state: 'I-tal' foods. Animal foods are dead foods and thus unhealthy as are inorganic and chemical foods. Tablets and medicines may be included in the latter category. Strict Rastafarian diets present problems for weanlings as nutritional knowledge and tradition are not well established within this community and poverty and adherence to expensive West Indian foods may restrict the diet excessively.

3.2.4 ZEN MACROBIOTIC

Here the Taoist philosphy of contrasting Yin and Yang foods is mixed with strict adherence to organic forms and 10 dietary regimens (−3 to +7) of increasingly restrictive stages. All concentrate on naturally grown foods. Meat is allowed in the lowest stages. With increasing stages foods are gradually withdrawn so that in the final stage the diet is the most elemental and natural—entirely whole grains. White sugar and sugar-containing items are avoided. Exotic foods tend to be prominent. Liquids are used very sparingly. Macrobiotic foods are encouraged for young infants instead of milk but the traditional infant formula derived from grains and seeds is grossly energy deficient and infant nutrition may be compromised before the weaning age is reached.

3.2.5 HARE KRISHNAS

These are lactovegetarians who again stress natural and unprocessed foods.

3.2.6 These last three relatively recently developed dietary cults, if followed strictly, can lead to major nutritional problems for weanlings. Unfortunately cult followers have often opted out of society and out of formal medical practices. Thus dietary help and advice from traditional sources—community dietician. general practitioner, health visitor—may be unacceptable. Nutrition education for group leaders may be important.

4 How to ensure a satisfactory vegetarian diet for weanlings

4.1 The basic principles of weaning as outlined in *Present Day Practice in Infant Feeding*[9] apply to vegetarian weaning as much as to weaning on to unrestricted diets.

4.1.1 Weaning diet should occur between 3 and 6 months in most cases and the introduction of non-milk, non-formula foods should be a gradual process.

4.1.2 Children's vitamin drops (vitamin A, 200 μg; vitamin C, 20 mg; vitamin D, 7 μg in five drops) should be given daily from 1 month until at least 2 years.

4.1.3 Breast milk or infant formula (cow or soy protein based) but not unmodified cow milk should be continued with the weaning diet in children under 1 year.

4.1.4 Growth of weanlings should continue to be monitored and plotted on standard centile charts as part of health surveillance and mothers advised appropriately if growth deviates from the expected.

4.1.5 Families should be encouraged to seek advice on vegetarian weaning diets from community dieticians, suitably trained health visitors or groups such as the Vegan Society (33/35 George Street, Oxford OX1 2AY).

4.2 ENERGY

At weaning the infant's main need is for a source of energy. If the energy intake is adequate, protein utilisation will be more efficient and essential amino acids and nitrogen will be conserved. Without adequate energy, amino acids must be metabolised to provide essential energy and nitrogen is lost from the body.

Provided infants continue to take about 500 ml/day of breast milk or infant formula, the needs for other protein will be relatively small. The energy density of many vegetarian foods is low, however, due to low fat and high fibre content. Small infants may have difficulty consuming the necessary volume of diet to achieve adequate energy intake. This situation can usually be avoided by:

4.2.1 Feeding infants frequently: weanlings should be fed at least four times a day.

4.2.2 Including energy dense weaning foods at each meal. Home prepared, but strained or homogenised, meals are often more energy dense than tins and jars of commercial weaning food. Cereals and pulses are usually more energy dense than fruits but ripe bananas have 15–20% carbohydrate and avocados are rich in fat (22 g/100 g) and thus good sources of energy (0·93 MJ (223 kcal)/100 g).

4.2.3 Controlling or increasing the energy density of foods by serving cereals as thick, rather than thin, porridge and/or adding fats to cereal meals. Fats added to cooked cereals prevent them solidifying quite so much on cooling.[10] Margarine and peanut butter (avoid crunchy peanut butter as this can cause inhalation of nut fragments) improve the energy density of bread. Oils mixed with flour in preparation of traditional breads improve energy density.

4.2.4 Preventing infants filling themselves with juice or milk formula before taking the main part of the meal.

4.3 PROTEIN

Many vegetable proteins are deficient in one or more essential amino acids. The total protein in vegetable foods is also low compared with animal protein sources. Legumes have the highest proportion of protein (over 20%). Soya beans are a very rich source achieving about 36% protein. The difficulties of achieving adequate protein nutrition of weanlings on vegetarian diets can be reduced by continuing a moderate intake of breast milk or cows' milk or soya protein based formula. A pint—or about 500 ml—per day breast milk or formula provides a quarter to a third of the year old infant's protein requirements as first class protein. Mixing milk or formula intake with vegetable protein foods enhances the amino acid composition of the meal and improves net protein utilisation.[10–12] Where breast milk intakes have fallen to low levels or where mothers wish to stop breast feeding, infants should be changed to standard infant formula (not cows' milk, which does not have added vitamins and iron) or to a totally animal product free soya protein isolate infant formula.

Not all soy protein infant formulas are free in animal fat but appropriate formulas are Formula S (Cow and Gate); Prosobee (Mead Johnson) and Isomil (Ross-Abbott). Soya formulas suitable for adults and obtainable from health food shops are not suitable for infants as they do not have added methionine, vitamins, and iron. They should not be fed to infants.

Protein needs can be met by:–

4.3.1 Maintaining moderate intake of breast milk, cows' milk based or soy protein isolate based infant formula together with vegetable protein foods.

4.3.2 Ensuring adequate energy intake so as to conserve nitrogen.

4.3.3 Planning meals so as to mix complementary proteins (examples below).[10]

4.3.4 Complementary protein foods:

Dairy products: high in lysine and isoleucine: complement cereals, nuts and seeds (avoid nuts and seeds except as very finely powdered preparations because of the risks of inhalation).

Legumes (beans, lentils, chick peas): low in tryptophan and sulphur containing amino acids but quite rich in lysine complement cereal grains, seeds and potatoes. (Legumes require prolonged soaking and cooking and mashing before they are digestible). Tofu, a pressed soya bean preparation, and soya milk yoghurt are useful in designing weanling diets.

Grains (wheat, oats, barley, rice, etc): low in isoleucine and lysine: use with milk, yeast or legumes, potatoes, and vegetables. Grains vary in amino acid composition and mixing grains improves net protein utilisation. Rice is richer in lysine than wheat. Spiked millet (bajra) has more balanced essential amino acids than maize (for example) and is particularly rich in iron and casein. Oats are the cereal with the most adequate amino acid content. All grains absorb water when cooked and this increases bulk while reducing protein concentration.

Dark green leafy vegetables: these only contain about 5% protein but are a good source of sulphur containing amino acids (and vitamin A). They complement legumes.

4.4 VITAMINS

4.4.1 Infant formulas (cows milk protein based or soy protein based) have added vitamins and iron and again should be consumed in preference to cows' milk for all vegetarian infants throughout the weaning period.

4.4.2 As recommended by the Department of Health and Social Security for all children,[9] children's vitamin drops (A, C, and D as above) should be given to vegetarian infants from usually 1 month old, and certainly from the introduction of weaning foods, until 2 (and preferably 5) years old.

4.4.3 The vitamins most likely to be deficient in vegetarian diets are B_{12}, D, and riboflavin. Lacto-ovo vegetarian diets usually have sufficient B_{12}, D, and riboflavin provided there is a substantial formula intake. Intake of vitamin D may be below recommended without harm *provided there is considerable exposure to summer sunlight.*[13 14] The main source of riboflavin is milk, and eggs and milk are both sources of B_{12}.

4.4.4 Vitamin B_{12} does not occur in plant products (with the exception of uncertain amounts in seaweed and fermented soya products). Strict vegans are thus theoretically at great risk of B_{12} deficiency. In practice clinical studies suggest that problems due to B_{12} deficiency are less common in vegan adults than might be expected.[15] This argument should not be used to suggest that weanlings on total vegetarian diets do not need supplementation. Fetal stores of B_{12} relate more to maternal B_{12} intake in pregnancy than to maternal B_{12} stores. The infant born to a total vegetarian mother may be born already deficient in B_{12}. Breast fed infants of total vegetarians are also likely to be receiving B_{12} deficient milk. Their need for supplementary B_{12} at weaning is critical. Various oral preparations (Tastex, Barmine 50 µg B_{12}/100 g) are available and these or another B_{12} supplement must be used. (Tastex and Barmine have high sodium content and should not be used excessively in infancy).

4.4.5 Vitamin D deficiency is common in vegetarian infants who have had little exposure to summer sunlight.[14] Often these are infants born to mothers with vitamin D deficiency. If breast fed, these infants will continue to receive D deficient diets as breast milk is always low in vitamin D and its relative content of vitamin D reflects maternal stores. The fetal state is compounded by postnatal deficiency. Vitamin D supplementation is thus advisable before weaning and supplementation at weaning becomes essential. In older children sunlight exposure should provide sufficient vitamin D to meet requirements by skin synthesis.[13] This cannot be relied on for weanlings particularly where minority group mothers tend to stay indoors keeping their young children with them.

Foods which are naturally good sources of vitamin D are liver, oily fish (sardines, herrings, mackerel), egg yolk and, to a lesser extent, dairy products with a high fat concentration: cheese and cream. All infant formulas, many infant cereals and other breakfast cereals, and margarines are supplemented with vitamin D. Infants on other than total vegetarian diets should be encouraged to use some of the animal sources in their diets. The main dietary source of vitamin D for weanlings is likely to be infant formula (cows' milk protein or soya protein based) and cereals. Margarines supplemented with both vitamin A (900 μg retinol/100 g) and D (8 μg/100 g) should be encouraged. Ovaltine is also a good source of vitamin D (31 μg/100 g). Ghee is not a good source of vitamin D.

4.4.6 Excessive vitamin intakes have no confirmed health advantages and may be dangerous. Recommended intakes of supplementary vitamins should not be exceeded.

4.5 MINERALS

4.5.1 Vegetarian foods may contain a wide variety of minerals sometimes present at quite high levels. Binding to phytates or other fibre in the gut or the form (for example, Fe^{+++} or Fe^{++}) in which the mineral is present inhibit mineral absorption from food. The bioavailability of the supplemental iron in commercially prepared infant cereals is uncertain.[16] In general vegetarian children require higher mineral intakes than children on mixed diets to achieve requirements[17] [18] as absorption of minerals from plant foods is often less efficient than from animal sources.

Iron and zinc are minerals particularly likely to be affected by binding in the gut.[17]

4.5.2 Egg yolk is a rich source of iron but eggs appear to inhibit absorption of non-haem iron eaten with them. Vegetable foods with high iron content are dark green leafy vegetables, lentils, chick peas, peas, molasses, and curry powder (it is not clear how efficiently the iron in curry powder is absorbed) The phytate content, particularly of the legumes, reduces the availability of iron in vegetables. Ascorbic acid-containing fruits and fruit juices may increase the availability of iron from vegetable foods. Most commercial orange squash (not infant preparations) does not contain ascorbic acid.

4.5.3 Many vegetarian diets are low in zinc and calcium. It may be difficult for weanlings to achieve adequate calcium intake unless they are maintaining reasonable intakes of breast milk or formula.[19] It is essential that vegetarian weanlings receive vitamin D supplementation so that the efficiency of calcium absorption is maximised.

5 Diets which are more restrictive than just excluding animal products

5.1 It is very difficult to achieve nutritional adequacy for energy, minerals, and certain vitamins in weanlings on strict fruitarian, Rastafarian, or macrobiotic diets.[20] Severe clinical malnutrition has been described in association with the use of such diets.[21] [22] We cannot recommend them.

5.2 Elimination diets seem largely unnecessary in the weaning age group. Even well designed elimination diets are likely to be deficient in calcium.[23] These diets should only be followed after medical recommendation and with paediatric dietetic support.

5.3 'Additive free' and 'organic' diets cannot be recommended without careful paediatric dietetic advice and supervision over foods which cannot be exchanged or avoided. Their use in the weanling age group is again very limited.

6 Summary: principles of achieving a satisfactory weaning diet for vegetarians

6.1 The basic principles of weaning outlined in *Present Day Practice in Infant Feeding*[9] apply to weaning vegetarian as well as omnivorous infants.

6.1.1 Weaning foods should be introduced gradually and not later than 6 months of age but not normally before 3 months of age.

6.1.2 Vitamin supplements (A, C, and D) as childrens' drops (five drops daily), should be given to all infants at least from the age of weaning, if not before, and until 2, and preferably 5, years of age.

6.1.3 All infants should be weighed regularly as part of health surveillance. Weights should be plotted on standard centile charts so that intervention can occur early if there is inadequate or excessive weight gain.

6.2 A moderately high intake of milk or formula should be maintained throughout the first year of life. This should be breast milk, cows' milk based infant formula, or soya protein based infant formula. Breast milk or infant formula provide significant protein and calcium and, with formula, vitamins. We cannot recommend cows' milk in the first year of life.

6.2.1 Infants should be fed frequently: at least four meals a day.

6.2.2 Diets should contain a variety of foods at each meal and different meals should utilise different vegetarian foods. Families should plan for each meal to contain food from a carbohydrate staple, a protein source, and then vitamin and mineral sources (food group or food square method).[10] A source of ascorbic acid should be provided at each meal to facilitate mineral absorption.

6.2.4 The energy density of foods is important. Adding fats to weaning cereals and other staples will improve energy density.

6.2.5 Avoid sating appetite with low energy juices before the meal.

6.2.6 Use margarine fortified with vitamins A and D rather than butter or ghee as fat source.

6.3 Total vegetarians require supplementary vitamin B_{12}. This should be provided either as proprietary preparations (Tastex, Barmine) or as an oral preparation once weekly.

6.4 The advice of community dietician and/or the Vegan Society should be encouraged particularly for those families weaning their infants onto total vegetarian diets.

6.5 More limiting regimens than total vegetarianism must be avoided in young children. Such regimens are likely to lead to unbalanced and grossly inadequate diets. Families who insist on feeding their children on such diets must be prepared to accept close supervision of their children and dietary supplementation when indicated.

6.6 The recommendations of the COMA report on reducing the total fat in the diet and encouraging fully skimmed milk,[24] do not apply to children under 5 and could be dangerous in weanlings. However, the Committee on Medical Aspects of Food Policy Panel on Child Nutrition has commented that 'where semi-skimmed milk is in general use in a home there are no strong objections to its progressive introduction from the age of 2 years, *provided the child's overall dietary balance is adequate.* Wholly skimmed milk should not be introduced before the age of 5 years.'[25]

We should like to acknowledge Anita MacDonald, Brenda Clark, Sadru Jivani, Jane Thomas, and Stephen Vickers for their helpful advice during preparation of this paper. We are also grateful to John Wilkins and Jim Smellie for typing and correcting numerous drafts of the manuscript

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A document produced by Dr EME Poskitt on behalf of the Nutrition Standing Committee of the British Paediatric Association.

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Hazards of analgesia for newborn infants

Sir,

Over recent months there have been many communications exhorting paediatricians and anaesthetists to prescribe analgesics for newborn infants.[1] [2] Such prescriptions are not without risk with problems mainly manifesting as respiratory or cardiovascular depression Indeed opiates are frequently used to stop an infant struggling against the ventilator. Little is known, however, about how preterm infants handle opiate analgesics. We therefore undertook a study of alfentanil pharmacokinetics in preterm infants undergoing paralysis and mechanical ventilation for respiratory distress syndrome. Alfentanil was chosen because of its rapid distribution and short half life in adults and older children. We were concerned that other drugs may have such prolonged excretion rates that accumulation might occur with repeated doses. For example, among preterm infants undergoing surgery for patent ductus arteriosus the half life of fentanyl may be prolonged to over 17 hours compared with two hours in adults.[3] There are no comparable data for other opiates. Our aim was to establish a regime for continuous infusion or safe regular bolus dosage

This study was approved by the local ethical committee. The pharmacological data will be reported separately. Recordings were made for 20 children, median gestation 30 weeks (range 25–36), median birth weight 1348 g (range 690–4084) at <24 hours age (n=10), 25–48 hours (n=5), and 49–84 hours (n=5). All children had indwelling arterial catheters and continuous direct blood pressure monitoring

The intravenous administration over two minutes of 20 µg/kg alfentanil produced a rapid and significant fall in both heart rate and blood pressure (table) Arterial oxygenation worsened but there was no change in $PaCO_2$ or pH. This occurred despite a smaller loading dose than the recommended 30–50 µg and slow intravenous injection.

In the preterm infant fluctuations in blood pressure and specifically hypotension have been associated with periventricular haemorrhage and periventricular leucomalacia. Although the sedative effect of opiates may reduce variability of blood pressure,[4] any hypotensive effect remains of great concern. Thus despite calls for the administration of opiates to ventilated preterm infants, we urge proper evaluation of their pharmacological and clinical effects before their use becomes widespread.

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Table *Physiological responses to 20 µg/kg alfentanil (n=20). Results expressed as median (range)*

Time	*Heart rate (bpm)*	*Mean blood pressure (mm Hg)*	*PaO_2 (kPa)*	*$PaCO_2$ (kPa)*	*pH*
Baseline	153 (127–193)	44·5 (25–55)	8·0 (4·7–12·9)	5·4 (2·8–9·9)	7·33 (7·03–7·39)
Baseline plus					
2 minutes	153 (129–194)	40·5 (30–54)			
3 minutes	151 (134–194)	37·0 (29–51)			
4 minutes	150 (131–193)	35·5 (29–49)			
5 minutes	149 (131–193)	35·0 (29–48)			
6 minutes	150 (130–193)	36·0 (28–47)	7·5 (4·4–13·3)	5·6 (4·5–9·2)	7·33 (7·21–7·38)
p Value	0·014	<0·0001	0·005	NS	NS

Significances of differences between baseline and 6 minute values tested with paired *t* test

Rearing children

Sir,

Your issue of May this year includes not only Dick Smithells enthusiastic review of *Child Health in a Changing Society*[1] but Walker's disturbing explication of government policy in relation to child benefits.[2] There are issues here which physicians for children, and indeed all who work in the field of child care, need first to think through and then to speak out about: only we have the professional attitude of disinterested concern about the nation's children that should enable us to spell out to the electorate where their government is taking us

Four things have to be taken into consideration: the first. that there are both religious and biological reasons why we should not even attempt to interfere with the freedom to reproduce, the second, that the way in which other people's children are reared will inevitably affect all of us as we or our children will have to live with them at school and when they grow up Too high a proportion of the inadequate, the unfit, and particularly the delinquent makes it difficult for a society to organise itself in a civilised way Thirdly, poverty, which is not all a matter of income—it can be a matter of the spirit as well as the pocket—makes the task of rearing a human child extremely difficult, and fourthly, the sins or inadequacies of parents should not be visited on their children. If this is all unquestionally so, as most of us would concede, it means that we have the duty to tell the public and the government they have elected that some of the latter's policies are likely in the long run to undermine our society and that we will therefore need to take preventative action in the short run—that is, now

Most parents would manage better with more money. especially if it were given specifically for the purpose of child rearing to their mothers; some families need the constraints of carefully drafted, well publicised, and sensibly enforced laws and regulations if they are to exercise their power over their children responsibly. All who contemplate taking on the enormous responsibility of bringing another human being into the world under the urge of biological imperatives should have been educated in what that will involve for them—and the children. Those inclined to abuse their children should know that this is unacceptable and will almost inevitably lead to their being held to account in some way. Those who have been improvident should be constrained in some other way than through their children's welfare into using their resources more wisely. And all of us should be persuaded that it is in our interests as well as a moral duty to do our best to improve the soul destroying environments in which so many of our children are brought or 'dragged up'. Perhaps buying cigarettes with money that should go on food or locking children up for a visit to a disco or pub are just the ways in which some parents, with very little in the way of inner resources, manage to keep going in the face of poverty, hopelessness, suppressed anxiety and a way of life that offers no joy, no security and little satisfaction—no 'love' or 'work', as Freud put it when defining maturity.

If we do not, to some extent, regard ourselves as our brothers' children's keepers for their childhood, we shall have to contain them when they grow up. What a good society offers is a framework in which it is possible for all of us to give of our best in the ordinary affairs of life and for all of us to have at least the opportunity to make the best and the most of it; and in this context we should not forget the children of the rich, if their parents end up giving them precious stones, when they ask for the bread that signifies manifest love, in the struggle to get the largest possible share of the wealth that work creates.

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Use of growth hormone

Sir,

We feel it is important to draw the attention of paediatricians in the United Kingdom to the following statement recently issued by the European Society for Paediatric Endocrinology regarding the therapeutic use of human growth hormone. According to the third listed recommendation, a mechanism to establish a national register of treated children in this country is to be implemented

In 1984 the European Society for Paediatric Endocrinology established a working party to consider the various implications of increasing availability of human growth hormone produced by recombinant DNA technology The same working party was also concerned with coordinating information, within Europe, when pituitary growth hormone was withdrawn in an increasing number of countries after the occurrence of Creutzfeldt-Jakob disease in several patients from the United States, United Kingdom, and New Zealand previously treated with this product.

There are now a number of human growth hormone products either licensed or undergoing clinical trial and there is every likelihood of rapidly increasing supplies over the next few years. The value of human growth hormone in the treatment of short stature due to classical growth hormone deficiency is incontestable, as for pituitary growth hormone, but its role in management of other indications is still far from certain. Among the latter the most important could include Turner's syndrome, non-endocrine short stature, and children of low birth weight Even in classical growth hormone deficiency there are still many uncertainties concerning diagnosis and optimal human growth hormone treatment regimen.

With these difficulties in mind, the working party has made the following recommendations·

(1) Until the remaining problems with treatment of classical growth hormone deficiency are resolved,

prescription of human growth hormone, even for this indication, should be controlled by those practitioners experienced in paediatric endocrinology

(2) The treatment of patients with other indications should be restricted to carefully designed protocols, within academic units experienced in such research.

(3) In order to allow long term surveillance of all patients treated with human growth hormone it is desirable that a mechanism to identify all such recipients be set in place such that they will be identifiable in a national register for the foreseeable future

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Inequalities in child health

Sir,

We turned with excitement to Michael Wadsworth's annotation[1] having awaited a response in the BPA's Journal to the recent reports which have highlighted the dramatic differences in children's health across the social classes and the increasing severity of child poverty in the United Kingdom [2-4] We were impressed with the evidence of the wide range of measures of health in childhood related to social background that have long term implications. We were disappointed, however, not to find guidance for paediatricians on the causes of the inequalities and on the action we should take individually and as an organisation to redress them.

It will be important to provide accurate evidence of demographic changes in child health, particularly as they affect child nutrition and growth so that the effects of interventions can be evaluated But surely paediatricians should also look to their response to inequalities now. We suggest that though action should be political and the BPA should make its views clear to government, this is not enough We must respond through the health service by analysing:

- The structure of our service—is it accessible and meeting people's needs? Do we collaborate sufficiently with other disciplines and offer training to primary care teams?
- The content of service delivery—are we emphasising prevention sufficiently, and do we work with deprived communities to meet their needs for health care?
- The outcome—do we attempt to measure the effect of our services on deprived populations and provide feedback to those who collect the data?

It would be tragic if the 1980s pass without paediatricians as a group making a concerted response to child poverty and health inequality.

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Phototherapy and the use of heat shields

Sir,

We read with interest the study of Dr Stutchfield and colleagues on the reduction of irradiance which occurs when heat shields are used.[1] In our own unit we had observed the apparently poor response to phototherapy of infants being nursed under transparent thermal blankets ('plastic bubble blanket'), and we therefore carried out measurements of the optical transmission characteristics of three types of bubble plastic including one in regular clinical use.

The measurements were made using a Perkin-Elmer 330 spectrophotometer in combination with an integrating sphere. In the wavelength range 350–700 nm we measured directly transmitted light, scattered transmitted light, absorbed light, and reflected light The total light transmitted varied from 71% at 350 nm to 77% at 700 nm At 450 nm, an effective wavelength for the photocatabolism of bilirubin, 74% of the light was transmitted, 26% being lost by absorption or reflection. This reduction in transmitted light is more than twice that reported by Stutchfield *et al.* Possibly, differences in our respective samples could account for this, although it should be borne in mind that our measurements were obtained under closed cell conditions in which there was no possibility of contamination by daylight entering at the blanket's edge Our measurements also showed that of the 74% of light transmitted by our samples, approximately 46% was scattered light which, due to its angle of incidence with the infant's skin, would be less effective than that normally incident at 90 degrees. Our findings lead us to concur with Dr Stutchfield and colleagues that thermal blankets will significantly reduce the effective irradiance of a phototherapy source

Commercial phototherapy units vary widely in their outputs in the 420–480 nm range, and these outputs are generally suboptimal.[1] [2] Many of these older phototherapy units are still in use We suggest the use of more modern light sources, which do reliably achieve the recommended minimum irradiance of 1 mW/cm², together with the avoidance of bubble plastic and other heat shields, whenever bilirubin concentrations are approaching exchange transfusion levels in very low birthweight babies. Heat and evaporative losses can be reduced instead by humidification.[3]

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Diarrhoea due to breast milk: case of fucose intolerance?

Sir,

We read with interest the report by Barfoot *et al.*[1] Firstly, we would question whether five watery stools a day in a normally growing breast fed baby is abnormal. If the pressure from the parents to do something was so great that a formula change was necessary, however, we accept that Pregestimil, and subsequently SMA, at least benefited the parents.

Secondly, the authors recommend that 'sugar chromatography should be carried out on the stools of all infants with unexplained diarrhoea before changes are made in the diet.' We suggest this is impracticable, for the following reasons The stool obtained must be liquid, and must be frozen within 15 minutes of leaving the rectum; this presents difficulties within a routine clinical setting, such as a district general hospital in England. In addition, the test may not be available at all centres. If the suggestion were followed to the letter, even the best organised laboratory would be inundated with tests.

It is true that in the patient described, using only the result of a test for stool reducing substances (Clinitest tablets) could have resulted in the mistaken diagnosis of lactose intolerance The appropriate lesson from this report is that the diagnosis of lactose intolerance in a breast fed baby should not be accepted without question It is of physiological interest that loose stools in breast fed babies may be due to oligosaccharides and their breakdown products, but the stool consistency tends to improve with time, and should not in general be taken as an indication to stop breast feeding

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Diarrhoea due to breast milk: case of fucose intolerance

Sir,

I was interested to read the case report from Barfoot *et al* on fucose as a possible cause of diarrhoea in a breast fed baby The authors finish by saying 'This type of intolerance to human milk is rare, and we could find no previously published reports'. Just 10 years ago in the same journal Whyte *et al* published a short report on exactly the same finding.[2] They went further than the current authors in identifying oligosaccharides including particularly fucosyl lactose in the stools of 85% of healthy breast fed infants

Barfoot *et al* offer no supportive evidence for their contention that their finding represents intolerance. It is common for healthy breast fed babies to have loose stools, and five a day is not that rare. As this baby was said to be gaining weight satisfactorily it could be argued that they did this baby a disservice by changing her to artificial feeds. Perhaps if they had read Whyte's paper this baby's mother would have been allowed to continue breast feeding and the effort involved in publishing their report avoided.

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Drs McEnery and Seakins comment:

Certainly, healthy breast fed babies may have frequent loose stools. While it is difficult to define pathological diarrhoea, this infant's diarrhoea was sufficient to get him admitted to hospital despite the adequate weight gain Both the mother and experienced ward staff felt that the infant's diarrhoea was excessive, despite my attempts to reassure them. Reducing substances were identified in the stools repeatedly, at a concentration of 1% The diarrhoea immediately resolved on changing to a succession of two other milks (Pregestimil and SMA), and has never returned since. If the baby had continued to be breast fed we do not know whether he would have thrived adequately. His mother declined my suggestion to resume breast feeding. In these circumstances, I believe, it is reasonable to assume that the milk oligosaccharides were responsible for the troublesome diarrhoea (associated with perianal soreness) and that he benefited by the change of milk

Our observations do not contradict those of Whyte *et al* but underline the importance of diet in the interpretation of analytical findings and of collecting samples before dietary or other therapeutic manipulations

'. . . officiously to keep alive'

Sir,

It is good to read articles such as those by Dr Walker and Professor Campbell, which are trying to achieve an appropriate ethical stance in the intensive care of newborn infants.[1] [2] I would entirely agree with Dr Walker that the patient should be treated as a person, the burden being the treatment and not the child. It is poor clinical judgment to continue with onerous and unrewarding treatment. Yet we must also beware of the denial mechanism by which parents and professionals can collude both in giving up too soon or going on too long. A study of perinatal psychology needs to be brought into the ethical debate too.

I also wonder whether it is a correct deduction on Professor Campbell's part to suggest that the incidence of stillbirth associated with spina bifida dropped in the early 1960s only because of the introduction of a more optimistic surgical approach. This could also have correlated with the advent of neonatal resuscitation It is hard for us to realise now that intubation and ventilation of infants was, at that time, a new skill in the labour ward. We need not paint ourselves blacker than we were!

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Withdrawal of iodinated disinfectants at delivery decreases the recall rate at neonatal screening for congenital hypothyroidism

Sir,

We recently reported transiently raised serum concentrations of thyroid stimulating hormone during early postnatal life in infants born to mothers whose skin had been disinfected with povidone-iodine (PVP-I) at delivery for epidural anaesthesia or caesarean section.[1] This transient impairment of the thyroid function was particularly severe in breast fed infants with a 25 fold increase in the recall rate at neonatal screening for congenital hypothyroidism, and was attributed to iodine overload due to the appreciably raised iodine content of breast milk in women treated with PVP-I [2]

Therefore, PVP-I was replaced in obstetrics by a non-iodinated skin disinfectant (chlorhexidine 0·5% in isopropanolol 70% (CHL)). We compared the frequency distributions of serum thyroid stimulating hormone concentrations at the time of screening in our whole population of healthy breast or bottle fed full term infants, before (n=4745) and during six months after (n=1178) replacement of PVP-I by CHL. We considered separately infants born to mothers without (group 1) or with (group 2) skin disinfection. The table shows that the replacement of PVP-I by CHL entirely abolishes the differences between groups 1 and 2 in. (a) the frequency distributions of neonatal thyroid stimulating hormone concentrations and (b) the recall rate at neonatal screening under suspicion of congenital hypothyroidism (serum thyroid stimulating hormone concentration >50 mU/l) after the type of feeding (levels of significance as compared with group 1: $p<0.01$). Except for the type of skin disinfectant used in the mothers, the two newborn populations studied presented with identical epidemiological characteristics; consequently, our observations further support the view that iodine overload and transient subclinical hypothyroidism in breast fed infants resulted from the use of PVP-I in the mothers.

In conclusion, iodine overload is a significant and often unrecognised cause of very transient hyperthyrotropinaemia ('false positive') at screening [3] Therefore, PVP-I should be carefully avoided in the neonatal period whenever possible, especially in areas like Belgium where, because of a rather low iodine supply in the population,[3] the newborns are particularly sensitive to the antithyroid effects of iodine excess.

Table *Comparison of povidone-iodine (PVP-I) with chlorhexidine in isopropanolol (CHL) for skin disinfection*

	Frequency (%) of serum thyroid stimulating hormone concentration (mU/l)			*% Of serum thyroid stimulating hormone concentration >50 mU/l (recall)*	
	<10	*10–50*	*>50 (recall)*	*Breast fed*	*Bottle fed*
PVP-I					
Group 1	97·2	2·7	0·1	0·1	0·0
Group 2	79·9*	17·6*	2·5*	3·1*	0·5
CHL					
Group 1	94·4	5·6	0·0	0·0	0·0
Group 2	94·0	5·7	0·3	0·3	0·0

*$p<0·01$.

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Staff changes

We thank Professor ED Alberman, Dr JMH Buckler, and Professor JO Forfar who have completed their periods of office as members of the Editorial Committee, for their conscientious and meticulous work for the Journal.

We welcome the following as new members of the Editorial Committee. Professor JK Lloyd, Nuffield Professor of Child Health at the Institute of Child Health, London, and President of the British Paediatric Association; Dr IA Hughes Reader in Paediatric Endocrinology in Cardiff: Professor POD Pharoah, Epidemiologist of the University of Liverpool; and Dr L Polnay, Senior Lecturer in Community Paediatrics at the University of Nottingham.

Dr Michael Silverman, who has been a member of the Editorial Committee for two years, has been appointed Associate Editor. Eleven years ago, he was appointed Senior Lecturer and more recently has been Reader at the Royal Postgraduate Medical School, Hammersmith Hospital, London. He has been convenor of the Respiratory Group of the British Paediatric Association. His extensive research of the physiology and pathology of respiratory disease has included both preterm infants and older children.

Archives of Disease in Childhood, 1988, **63,** 1299–1300

Book reviews

The Genetics of Renal Tract Disorders. By M d'A Crawfurd Pp 663: £65·00 hardback Oxford University Press, 1988. ISBN 0–19–261147–X

A single author text which provides a comprehensive review of a difficult subject is a rare find. The author is a senior clinical scientific officer and consultant clinical geneticist at Northwick Park Hospital and has brought together a wealth of information in a unique contribution to the literature

In order to cater for clinicians, pathologists, and genetics staff there are introductory chapters on basic genetics and the structure and function of the renal tract. Other chapters provide extensive information on the genetics of both primary renal and urinary tract problems as well as detailing the renal involvement in a variety of uncommon syndromes and inherited metabolic diseases. There is a tendency to catalogue rather than synthesise the information but the text is extensively referenced and on some subjects there is more information than is available in specialist renal textbooks. The slight paucity of illustrations will not deter those who will use the text as a reference source The book is sufficiently up to date to mention the recent advances with gene probes for conditions such as adult polycystic kidney disease, but those who require guidance on the implications of the 'new genetics' will have to turn to more recent review articles.

This book will remain a reference source for a long time to come and its cost will ensure that it will find its way onto many bookshelves including those of paediatric departments.

A R WATSON

Basic Adolescent Psychiatry. By D Steinberg Pp 279. £25 hardback, £14·95 paperback Blackwells Scientific Publications, 1987 ISBN 0–632–01824–0

This book covers the classical psychiatry of adolescence in a competent and authoritative manner After sections on classification and assessment the main psychiatric disorders of this age group are described clearly and well, and there is a final chapter on general principles of management. The author is an experienced psychiatrist who writes from a good knowledge of the literature as well as from practical experience

It is therefore something of a disappointment to realise that the book will probably not be found particularly useful by paediatricians dealing with adolescents with psychosocial aspects to their illnesses There is a brief chapter on physical and psychosomatic problems, but it is sketchy and somewhat out of balance To dedicate just a few lines each to common problems such as obesity and uncontrolled diabetes, but half a page to Addison-Schilders disease seems eccentric There are some important omissions· in particular, there is virtually no discussion of the ways in which adolescent psychiatry can be integrated into adolescent medicine. It is unfortunate that the psychiatry of adolescence has become so separated from adolescent medicine for psychiatrists do, I believe, have much to contribute to an understanding of chronic disorders suffered by teenagers.

P J GRAHAM

Your Child Needs You: A Positive Approach To Down's Syndrome. By Joyce Mepsted. Pp 96: £5·96 paperback Northcote House, 1988 ISBN 0–7463–0511–7

This book by Joyce Mepsted, a special needs teacher, aims to provide information and positive and encouraging support for parents of children with Down's syndrome. After a foreword by Rex Brinkworth and a short introduction there are five main chapters, covering the stages from birth through to leaving school Each chapter has a somewhat emotional title 1, Fear and Prejudice; 2, Tears and Smiles; 3, Exploding the Myth, 4, The Door of Opportunity, and 5, The Ultimate Responsibility There are clear subheadings to each section and at the end of the first four chapters there is a detailed check list covering the developmental steps of that age period, resources, useful activities, and a few other general notes of advice

Mrs Mepsted often does not stay within this clear framework, however, and the text of the first two chapters particularly strays from the intended subject matter and becomes both repetitive and confusing. In part I think this is the result of her rather determinedly chatty style. Very 'positively helpful' advice can become positively cloying in nature, while in contrast some of the descriptions of problems are unnecessarily disheartening The picture of a floppy, snuffly, semipermanently deaf baby with an enlarged and thickened tongue would most certainly fulfil the very fears and prejudices she is trying to avoid There is insufficient advice about treatment and none about sometimes severe but correctable vision defects.

These criticisms certainly do not apply to the third chapter on starting school Here the author is on firmer ground and gives a clear account of the range of provisions available under the 1981 Education Act and the procedures involved in statementing, but she does not specify the statutory ages when this can be requested In the preceding chapter, clearer and more up to date details of financial allowances would be helpful.

The later sections provide useful but rather surprisingly limited advice about the prospects open to school leavers In the United Kingdom of Mrs Thatcher in the late 1980s, however, perhaps it is best not to look further than the traditional adult centre or sheltered workshop for these young people, as even the most able of us may never obtain full employment.

B EDWARDS

Raising a Handicapped Child. By C Thompson Pp 273. $7 95 paperback Ballantine Books, 1986 ISBN 0–345–34819–2

This book is designed to provide both advice and support for parents of handicapped children. It has been written with care and great sensitivity by an experienced paediatrician who is the director of the Center for Handicapped Children and Teenagers in San Francisco. Topics covered by the book include. the grieving process, dealing with family and friends, obtaining social and professional help, siblings, adolescence, therapy and medications, progressive disorders, and death. The author has adopted a positive approach throughout and this is reinforced by the chapters on 'How to help your child find some fun in life' and 'Success stories'.

Unfortunately, I do not think the book crosses the Atlantic well enough to be generally recommended for parents in the United Kingdom They would encounter some difficulties with terminology (shower parties), and major differences in both concepts (professional counselling, choosing a physician) and resources (20% of the book covers United States facilities for the handicapped while the 1981 Education act is, of course, not covered). There is much in the book to be admired, however, and I think that paediatricians in the early stages of their careers would benefit from the insights it offers into the problems faced by the handicapped and their parents

N J WILD

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The Journal of the British Paediatric Association

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Archives of Disease in Childhood, 1988, **63**, 1423–1425

Annotations

Diagnosis of tuberous sclerosis

Tuberous sclerosis was first clearly documented in 1880 by Bourneville (hence Bourneville's disease or epiloia) who described the typical pathological features—areas of sclerosis and other areas of tuber like growths at postmortem examination—in patients with mental retardation and fits.[1] For years the disease was only suspected in those suffering from mental retardation and fits but it is now known to occur in individuals of normal intelligence both with or without fits. The classic paper by Bundey and Evans brought this to attention by confirming that the disease is dominantly inherited often from unsuspecting parents who nevertheless have signs of the disease.[2] The incidence was thought to be one in 100 000 but the best estimate[3] has been recently updated (R H Lindenbaum, personal communication) to suggest one in 10 000. Mental retardation is thought to affect 50% of individuals with fits occurring in about 80%.

Clinical manifestations

The disease is now known to cause a plethora of abnormalities in a variety of organs.[4]

SKIN

The classic white patches are ash leaf in shape: these are often only seen in a dark room with an ultraviolet lamp and are the most common early sign.* Unfortunately 2–3 per 1000 of apparently normal newborn babies also show these patches.[5] Depigmented lesions may affect the hair, eyebrows, eyelashes, or even iris. The facial lesions are histologically angiofibromas, not adenoma sebaceum as at first thought. Angiofibromas affect the cheeks, nasal folds, and chin but often spare the upper lip: they are rarely present before 2 years of age and may not occur until after puberty, if at all The forehead fibrous plaque (a smooth patch of slightly raised skin with a reddish discolouration) is common and can be the first sign of the disease.[6] Shagreen patches usually occur from puberty and are leathery discoloured patches predominantly on the trunk, often in the lumbar region. Cafe-au-lait patches are not a sign of tuberous sclerosis.[7] Fibromas most often affect the nails of both hands and feet, causing deep groves, but can also occur in the gums around the teeth. The teeth can also be pitted [8]

NEUROLOGY

Fits are the most common presenting symptom and most often begin in the first year of life. They can be partial (focal) or generalised tonic-clonic but are frequently infantile spasms where up to 20% of cases are due to tuberous sclerosis.[9] Mental retardation is extremely rare without fits and usually becomes apparent in the first year of life. The fits are often resistant to treatment but control should be attempted.

The intracranial lesions are astrocytomas on histological examination and are usually benign, often calcifying. They characteristically line the lateral walls of the lateral ventricles but they can be found in the cerebrum and cerebellum, normally in association with more typically sited lesions Obstruction at the foramen of Monro can cause hydrocephalus. Infrequently malignant giant cell astrocytomas occur: these are thought to enhance with contrast injection on computed tomography.[10] The incidence of intracranial lesions is high even in asymptomatic patients and the advent of cranial computed tomography allowed easier early diagnosis in those presenting with fits. Not all paraventricular calcification is due to tuberous sclerosis but the multiple discreet nodular areas of calcification are fortunately fairly typical. A very early scan (the first six months of life especially) is not always reliable and may need to be repeated: up to 10% are normal initially. Transfontanellar cranial ultrasound scanning can be helpful even showing signs before they are visible on a computed tomogram,[11] but the reliability of this test is not yet certain The place for scanning by nuclear magnetic resonance is not yet established but the demyelinated areas would be expected to show up more often: they are not, however, diagnostic but might perhaps relate to the severity of retardation.

Mental retardation is often severe with no verbal communication and appreciable autistic features making caring difficult. By adolescence there can be a clear cut improvement in the autistic features but behaviour disturbance in a fully grown mobile but non-communicating young adult with tuberous sclerosis can be the biggest problem for many parents.

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*A hand held ultraviolet light costing approximately £12 is available from the secretary of the Tuberous Sclerosis Association, Mrs Janet Medcalf, Little Barnsley Farm, Catshill, Bromsgrove, Worcester B61 0NQ, from whom an illustrated medical leaflet will soon be available

EYES

Retinal phakoma are astrocytomas and are most easily seen when they calcify, appearing like great white tumours in any part of the retina They are therefore best looked for in dilated eyes, preferably by indirect ophthalmoscopy; they can be mistaken for retinoblastoma in young children, and when this diagnosis is considered the child should be examined for other signs of tuberous sclerosis to prevent unnecessary enucleation. It is extremely uncommon to find retinal phakomas as the only sign of tuberous sclerosis.

HEART

The disease can also cause cardiac rhabdomyomata, which are now known to be much more common than previously thought.[12] They are visible on echocardiography but are more easily seen in children than adults both for technical reasons and because they can reduce in size with age. Overt arrhythmias are uncommon, but the rhabdomyomata can cause cardiac failure in infancy. It is quite possible that all cases of cardiac rhabdomyomata are due to tuberous sclerosis but this has yet to be demonstrated

KIDNEY

Renal cysts (bilateral) can cause infantile polycystic disease. Angiomyolipomas also occur in the kidney more often in adults than in children.[13] When multiple they are diagnostic. Renal failure is rare and usually due to cysts.

BONES

Bony changes include cysts, periosteal new bone, and areas of sclerosis, but they are rarely symptomatic.[14] They are usually found in those in whom the diagnosis is obvious clinically.

Diagnosis

Making the diagnosis of tuberous sclerosis in an individual is therefore dependant on careful clinical evaluation (angiofibromas and ungual fibromas are probably diagnostic) including ultraviolet light with special investigations (cranial computed tomography, indirect ophthalmoscopy, and less frequently renal ultrasound and echocardiography) when necessary. Gomez produced diagnostic criteria,[13] which require modification (table): these are supposed to be a helpful guide not a rigid list of rules. Rarely, for instance, an obligate carrier has only a 'secondary' sign, such as white patches, whereas the presence of white patches in a young child with fits does not guarantee tuberous sclerosis: confirmation, often by a cranial computed tomogram would be wise.

Table *Diagnostic features of tuberous sclerosis**

Definitive diagnosis (primary features—only one required)	*Presumptive diagnosis (secondary features—two required)*
Classical shagreen patches	Hypomelanotic macules
Ungual fibroma	Gingival fibromas
Retinal hamartomata	Bilateral polycystic kidneys
Facial angiofibromas	Cardiac rhabdomyoma
Subependymal glial nodules (on computed tomography)	Cortical tuber (histological)
Renal angiomyolipomata	Radiographic 'honeycomb' lungs
	Infantile spasms
	Myoclonic, tonic or atonic seizures
	First degree relative with tuberous sclerosis
	Forehead fibrous plaque
	Giant cell astrocytoma

*Modified from Gomez.[13] This is for guidance only, clinical judgment is still often required

Genetics

With the discovery in 1987 that the gene for tuberous sclerosis is on chromosome 9,[15] linked to the gene locus for the ABO blood group, tuberous sclerosis could be said to have come of age. The gene was provisionally assigned to 9q34 at the eighth international conference on human gene mapping but this has not been confirmed by studies in the United States of America where heterogeneity was suggested[16]; however, no clinical evidence for this has yet been found. The variability of expression of the disease can be extreme but often occurs within a family the variability affecting all clinical features. Linkage has now been shown to a DNA polymorphism detected by v-abl[17] and an antenatal diagnosis performed using this marker.[18] More recent data suggest that this is not a sufficiently close marker for reliable antenatal detection,[19] but the evidence from the United Kingdom still suggests that the tuberous sclerosis gene locus is on chromosome 9 at q34. With the discovery of more tightly linked markers, antenatal diagnosis will become a reality Blood should be stored now for later analysis from any relevant family member, affected or unaffected, who is likely to die, and where antenatal diagnosis may later be required.

Familial cases are the minority and up to 80% of cases are new mutations occurring to normal parents. What investigations are required to exclude the diagnosis in parents? Clearly a detailed dermatological examination, including ultraviolet light examination, is essential as is ophthalmic examination which is non-invasive. Sporadic reports suggest that cranial computed tomography may pick up further cases[20 21] but even nuclear magnetic resonance imaging and other detailed investigation may fail to detect any evidence of disease in apparent obligate carriers.[22] This may represent germinal mosaicism rather than incomplete penetrance. The risk of recurrence of 1–2% in those normal on full investigation is probably much the same as for those normal on skin and eye examination only, but it is still perhaps wise to request cranial computed tomography.

Siblings of apparently isolated cases should be encouraged to have skin and eye examinations before being told that there is no recurrence risk because their parents are normal. Occasionally the only sign of disease is a fibroma of the nail. A single ash leaf patch probably remains the most common ambiguous clinical sign. As an incidental finding it should be ignored—in isolation it is not diagnostic but it is considered by some to be sufficient to make the diagnosis in an individual with a first degree relative with tuberous sclerosis. An intragenic marker might help to clarify the situation on those occasions where signs are in doubt and this may be available within the next decade as details of the gene locus are unravelled.

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Archives of Disease in Childhood, 1988 **63,** 1426–1427

Diseases caused by the human parvovirus B19

Parvoviruses consist of single molecules of single stranded DNA surrounded by non-enveloped protein coats. They affect a wide range of animals (cats, dogs, rats, pigs, cattle, mink, rabbit, geese) and cause, in some of them a variety of diseases (panleucopenia, cerebellar ataxia, enteritis, myocarditis, renal failure, fetal loss). B19 is the first human parvovirus. It was discovered in 1975 but has only been extensively investigated since 1980 when it was realised that it was the cause of appreciable human disease.

Occurrence of B19 infection

This is a common infection; about 70% of adults have serological evidence of past infection. Antibody is most commonly acquired between the ages of 5 and 15 years. The peak incidence of infections is in March, April, and May each year and epidemics tend to occur every three to five years. The infection is almost certainly worldwide as it has been found in every country (Europe, Scandinavia, America, Japan, Australia) where adequate studies have been done. Virus is infectious when given as nasal drops and the natural mode of transmission is almost certainly via the respiratory route from individuals incubating the infection. One week after exposure large amounts of virus are found in the blood for two or three days. At this time minor non-specific symptoms and any related to bone marrow failure (see below) occur. After about another week there is a second phase of illness characterised by a transient maculopapular rash or joint involvement, or both. At this stage there is a vigorous immune response, excretion of the virus has ceased, and the individual is immune for life.

Rash illness due to B19 infection

As with all common virus infections there is a wide range of disease. Wholly subclinical infections occur, more commonly in children than in adults. Infection with B19 may cause a wholly non-specific disease with a mild, transient fever and respiratory tract symptoms. The most common clinical symptom of infection is an erythematous rash to which a variety of diagnostic labels will be applied depending upon the nature of the rash and the context of its occurrence.

Erythema infectiosum or fifth disease (so called because it was the fifth of six childhood exanthems in an old classification) was first described about 100 years ago. There are usually no immediately prodromal symptoms but fever and mild respiratory tract symptoms may have occurred a week before. The rash begins with intense erythema of the cheeks (hence the synonym, slapped cheek disease). The edges of the red areas tend to be raised and there is relative circumoral pallor. The rash then appears on the arms and the legs as a discrete maculopapular erythema. The rash may become confluent in areas and then clears from the centre giving a lacy or reticular appearance especially over the lower limbs. The rash usually clears after a day or two but then has a tendency to recrudesce when the infected individual gets hot after exercise, bathing, or in sunlight.

Cases and outbreaks of erythema infectiosum throughout the world have been shown to be due to B19 infection. This particular diagnosis is usually made when there is a prominent slapped cheek component, or a lacy appearance to the rash or when an outbreak of such illness occurs in primary school children. The slapped cheek appearance does not always occur, however, and is particularly uncommon in adults. In such cases a diagnosis of rubella is often made and the other common clinical diagnoses in cases of B19 infection are allergic rash or unspecified viral rash Lymphadenopathy is found more often in rubella but joint involvement is common in both infections (see below) and the seasonal incidence of the two is the same. Specific laboratory tests are the only way of distinguishing precisely between rubella and B19 infection.

The rash associated with B19 infection is not always erythematous. The occasional patient with recent B19 infection will present with easy bruising or purpura Some have low platelet counts but most do not. The occasional case diagnosed clinically as Henoch-Schonlein purpura has been shown to be a recent B19 infection.

Joint involvement in B19 infection

Joint involvement has long been recognised as a complication of erythema infectiosum and with the advent of specific laboratory tests for B19 infection it is clear that this infection causes arthritis and arthralgia. In many respects it is equivalent to the arthropathy seen in rubella infections. It may occur with an erythematous rash or may be the sole presenting symptom. It occurs in only 5–10% of B19 infections of children but in 80% of infections in adult women. It usually involves the joints of the hands and wrists but may also involve knees and ankles. Arthralgia is the most common complaint but the joints are often stiff and swollen. In most instances the joint symptoms resolve within two weeks but in a small number of cases the symptoms may persist for months or years. Initially some patients have been classified as early rheumatoid arthritis but there is no evidence that B19 virus causes this disease.

Haematological changes in B19 infection

B19 virus infects the red blood cell precursors in the bone marrow and there is a cessation of erythropoiesis for about one week. This occurs in all persons infected with the virus but in haematologically normal people with haemoglobins of 110–140 g/l and red cells with a life span of 120 days there are no clinical effects, although the haemoglobin concentration temporarily drops by about 10 g/l. In those with chronic haemolytic anaemia, however, with an already low haemoglobin (steady state concentrations of 70–100 g/l) and red blood cells with a short life span (about 20 days) there is a temporary fall in haemoglobin to very low values and the patient is ill with the symptoms and signs of profound anaemia, which may require blood transfusion. This is called an aplastic crisis and is particularly a feature of sickle cell anaemia and hereditary spherocytosis. Over 95% of all cases of aplastic crisis that have been adequately investigated have been shown to be due to B19 virus infection and most occur in children under 15 years of age.

B19 virus infection in pregnancy

A transient but intense viraemia occurs as part of every B19 infection and should this occur during pregnancy there will be an opportunity for the virus to spread to the placenta and fetus. There is no doubt that B19 does cause fetal infection. It does not appear to cause birth defects like rubella virus infection but is a cause of loss of the pregnancy. If this occurs early in pregnancy it will be a spontaneous abortion and B19 infection appears to increase the likelihood of this threefold. If maternal B19 infection occurs in the second or third trimester it may be associated with hydrops fetalis due to a persistent fetal infection. This may result in late abortion or stillbirth. At present there is no need to alter the management of pregnancies complicated by B19 infection. The pregnancy may be lost but if it is not then a normal baby can be anticipated, although in many instances follow up has been for only a relatively short time.

Diagnosis of B19 infection

The common rash, illness and joint symptoms occur at a time when virus can no longer be detected in serum or throat swabs in most cases. Diagnosis is therefore based on the detection of B19 specific IgM antibody that is present in serum for two to three months after infection. Past exposure (and therefore immunity) can be assessed by testing for specific antibody of the IgG class. This diagnostic approach is exactly that used for rubella and a clotted blood sample with full clinical details is all that is required to investigate suspicious rashes. Virus may still be present in the serum in cases of aplastic crises and should be looked for by immunological or molecular biological techniques. Detection of virus is the only satisfactory method of diagnosing B19 infection in hydropic fetuses.

Unfortunately there is still a severe shortage of reagents for B19 virus diagnostic tests and these are only available in a limited number of centres. Hopefully in the near future synthetic antigens will become available. Diagnostic antibody tests could then be applied on a much wider scale.

For further details the reader is referred to the following reviews and textbook descriptions.

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Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis

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SUMMARY Forty four children with recurrent obstructive episodes after acute bronchiolitis in infancy were treated with nebulised beclomethasone dipropionate or placebo for eight weeks in a randomised double-blind study. They were seen monthly for a year afterwards, and also if they had acute respiratory illnesses with or without bronchopulmonary obstruction. The two treatment groups were well matched. The children receiving active treatment had significantly fewer symptomatic respiratory illnesses and fewer episodes of bronchopulmonary obstruction during the follow up period. The children given placebo had significantly higher obstructive scores during the study period, and they were treated with inhaled β_2 agonists and theophylline for longer periods of time during the follow up period.

The results suggest that nebulised beclomethasone dipropionate may have prolonged effects on subsequent asthmatic symptoms after termination of treatment in children with recurrent obstructive episodes after acute bronchiolitis.

Acute bronchiolitis in infancy is most often associated with respiratory syncytial virus infection, and is associated with later episodes of bronchopulmonary obstruction and the development of bronchial asthma in children.[1] [2] Inhalation of beclomethasone dipropionate, as an aerosol or as powder, is effective and safe prophylaxis of childhood asthma,[3] [4] possibly because it reduces the non-specific bronchial hyperreactivity in asthma.[5] As the use of both aerosols and powder inhalation is difficult in infants and small children, we have investigated whether nebulised beclomethasone dipropionate could be used in infants and small children with recurrent episodes of bronchopulmonary obstruction after acute bronchiolitis, and whether treatment with beclomethasone dipropionate for eight weeks could possibly influence the outcome. We have therefore conducted a placebo controlled double blind study in children under 2 years of age to study the effect of inhaled nebulised beclomethasone dipropionate for eight weeks with a follow up period of one year. The aim of the study was to examine whether inhalation of nebulised beclomethasone dipropionate influenced the frequency of recurrent attacks of bronchopulmonary obstruction during treatment, as well as the subsequent development of episodes after the treatment.

Patients and methods

A total of 44 children aged between six and 24 months were randomly allocated to be treated by placebo (n=22) or beclomethasone dipropionate (n=22) in a double blind manner. To be included in the study the patients had to fulfil the following criteria: they had to be previously admitted to the paediatric department of Ullevål hospital (the municipal hospital of Oslo) with acute bronchiolitis, and they had to have had a history of at least one attack of bronchopulmonary obstruction after the initial attack of bronchiolitis. The diagnosis of bronchiolitis was made according to the criteria of Court.[6] Table 1 shows that the groups were comparable. To diagnose an episode of bronchopulmonary obstruction three of the following signs were required: wheezing, expiratory dyspnoea, paradoxical chest movements on inspiration, rapid respiratory rate (>40 a minute) and audible râles and sibilant rhonchi.[2] Children were not included in the study if they had other serious disabling diseases or had received prolonged courses of systemic treatment with steroids. Children who had received steroid treatment for only a few days during previous severe attacks of bronchopulmonary obstruction were included.

Double blind parallel groups received either

Table 1 *Clinical details of children treated with nebulised beclomethasone dipropionate (n=22) and placebo (n=22) Figures given are mean (SEM)*

	Placebo	*Nebulised beclomethasone dipropionate*	*p Value (two tailed)*
Age at inclusion (months)	17 3 (0 9)	14 1 (1 2)	0 09
Birth weight (g)	3300 0 (200)	3300 0 (200)	0·99
Duration of breast feeding (months)	6 1 (1 3)	5 6 (0·9)	0 66
Weight at inclusion (kg)	11 2 (0 3)	10 1 (0·4)	0 05
Height at inclusion (cm)	80·5 (1·0)	77·6 (1·4)	0 21
No of respiratory illnesses at inclusion	7 9 (0 7)	6 1 (0 6)	0 09
No of lower respiratory infections at inclusion	3 5 (0 4)	4 3 (0·6)	0·52
No of episodes of bronchopulmonary obstruction at inclusion	4 8 (0 6)	4 4 (0 6)	0 55
No of courses of antibiotic treatment at inclusion	3 9 (0 7)	3·9 (0 6)	0·86
Boys girls	15 7	18·4	0·29

placebo or beclomethasone dipropionate, and the children were stratified in six blocks according to the number of previous attacks of bronchopulmonary obstruction (one or two attacks, three or four attacks, and more than four attacks) they had had as well as according to whether or not respiratory syncytial virus was detected in their sputum during the first episode of bronchiolitis. Each of these six blocks were randomised separately in such a way that half the patients within each block was given beclomethasone dipropionate and the other half was given placebo, in order to obtain a balanced design.

The patients were randomly allocated to receive either placebo or active treatment with nebulised beclomethasone dipropionate. Identical bottles contained either an aqueous suspension of beclomethasone dipropionate 50 μg/ml or placebo solution containing the preservatives and buffers of the active suspension. The patients were supplied with the PaRi Inhaler Boy nebuliser (Paul Ritzau Pari-Werk GmbH) for home treatment and received a dose of 2 ml four times daily for the first two weeks, and then 2 ml twice daily for the remaining six weeks. The patients also received additional treatment for bronchopulmonary obstruction according to the standard clinical practice of the hospital. During the follow up period the patients were seen regularly each month, and on additional occasions if they had an acute respiratory illness with or without bronchopulmonary obstruction. Whenever they were seen a questionnaire was filled in by the examining doctor, and a score of the degree of bronchopulmonary obstruction was obtained during acute attacks (table 2). The maximum possible score at any one visit was 15.

At the end of the study period allergic reactions were sought by skin test, radioallergosorbent test (Phadebas, RAST), and measurement of total IgE (Phadebas, PRIST). The skin test and the RAST tests were carried out as reported in a previous study.[7]

When respiratory tract illnesses occurred, nasopharyngeal aspirates were obtained and examined for respiratory viruses by rapid immunofluorescence and cell culture as previously described.[7] This was also done during hospital admissions before the study.

The results are given as medians with 95% confidence intervals calculated by the Bernoulli-Wilcoxon method.[8]

Table 2 *Score used in the evaluation of the patients during episodes of bronchopulmonary obstruction*

Variable	*Score*
Respiratory rate.	
<40/minute	0
40–60/minute	1
>60/minute	2
Rib retraction, use of accessory respiratory muscles, wheeze, rales	
None	0
Moderately affected	1
Definitely obstructive	2
Chest radiograph.	
Not performed or normal	0
Hyperinflation or increased translucency	1
Consolidation or atelectasis	2
Capillary blood gases	
Not performed or normal	0
PCO_2 between 6–7 kPa	1
PCO_2 >7 kPa, pH <7·3	2
General condition	
Not affected, playing normally	0
Pallid, moderately affected	1
Severely affected, cyanotic	2
Treatment score	
No bronchodilator	0
Epinephrine aerosol or inhaled salbutamol	1
Intravenous theophylline or steroids	2
Artificial ventilation	3

Both one and two tailed tests were used. Differences were considered significant when the p values were less than or equal to 0·05. The significance of differences between groups was tested by the Wilcoxon midrank sum test.[8] Time until the first symptomatic respiratory illness and the time until the first episode of bronchopulmonary obstruction were both calculated by the Kaplan-Meier estimate[9] and Gehan's statistic.[10]

The parents of the participating children received oral as well as written information about the aims and the means of the study and gave informed written consent before the children were included in the study which was conducted according to the Declaration of Helsinki as revised in Tokyo, 1975. Approval for the study was obtained from the national committee on drugs of Norway and by the local ethical committee of Ullevål hospital.

Results

Twenty two children were randomised to receive placebo and 22 to receive beclomethasone dipropionate. There were no significant differences between the two treatment groups in the incidence of neonatal respiratory disease (p=0·31), or allergic disease among the mothers (p=0·52), the fathers (p=0·40), the siblings (p=0·31), or the grandparents of the patients (p=0·52). This was true also for other pre-existing diseases among parents, siblings, and grandparents. In addition no significant differences were found for family relationship (p=0·47), number of siblings (p=0·40), hygienic state of the home (p=0·20), floor covering in the homes (carpets or not) (p=0·55), pets in the home (p=0·12), place of stay during the day (for example kindergarten, nursery, at home) (p=0·66), and tobacco smoking in the home (p=0·95). Other background variables are given in table 1. The children in the placebo group were generally older and heavier than the treated children at the time of inclusion in the study. They also had more acute respiratory tract illnesses before their entry in the study, though the difference was not significant. There were no differences in the number of lower respiratory tract infections, the number of episodes of bronchopulmonary obstruction or the number of courses of antibiotics (table 1). Previous history of respiratory virus infections before the inclusion in the study did not differ between the two groups. Fifteen children in the placebo group and 18 in the treated group had no history of previous virus infections. Of those with a history of previous virus infection, respiratory syncytial virus had been found in three children in the placebo group and in two in the treated group, adenovirus in two in the placebo group and one in the treated group, rhinovirus in three in the placebo group and parainfluenza virus infection in one in the treated group.

No child was withdrawn during the eight weeks of treatment with beclomethasone dipropionate or placebo, and no side effects were observed in either group. During the follow up period one child was withdrawn from the study, and two children dropped out. One child who received beclomethasone dipropionate was withdrawn because severe symptoms occurred a few weeks after stopping the inhalation treatment, and because of this the randomisation code was broken. This child was included in the statistical evaluation of the results with the least favourable results in the beclomethasone dipropionate group. One child who was also receiving beclomethasone dipropionate dropped out of the study because the family moved to another part of Norway during the follow up period. Another child who was receiving placebo dropped out shortly after inclusion in the study because the wrong inclusion criteria had been applied. These two subjects were not included in the statistical evaluation of the results, and were replaced by other children.

The results of treatment with nebulised beclomethasone dipropionate compared with placebo are shown in table 3. The time from the start of treatment until the first acute symptomatic respiratory illness and until the first episode of bronchopulmonary obstruction were significantly longer in the beclomethasone dipropionate group. The probability of not contracting an acute symptomatic respiratory illness from the start of the treatment for the two groups of patients is shown in fig 1, and the probability of not contracting an episode of bronchopulmonary obstruction is shown in fig 2; the probabilities for both variables were significantly higher in the beclomethasone dipropionate group. The placebo group also had significantly more symptomatic acute respiratory illnesses and more episodes of bronchopulmonary obstruction during the study period (table 3). They also had a significantly higher total mean obstructive score during the study period, whereas the mean obstructive score for an episode did not differ between the two groups (table 3). The placebo group did not, however, have more respiratory virus infections diagnosed than the beclomethasone dipropionate group (p=0·24). In the placebo group three respiratory syncytial virus, four rhinovirus, one adenovirus type 2, and one parainfluenza virus type 3 infections were diagnosed, whereas in the beclomethasone dipropionate group six respiratory syncytial virus, one rhinovirus, one adenovirus type 2 and one parainfluenza virus type 3 infections were diagnosed.

Apart from the double blind treatment with

Table 3 *Observations during active treatment period and during follow up period. Figures given are median (95% confidence interval)*

	Placebo	*Nebulised beclomethasone dipropionate*	*p Value (one tailed)*
Time until first symptomatic respiratory illness (weeks)	4·0 (2 to 8)	7·5 (2 to 23)	0·035
Time until first episode of bronchopulmonary obstruction (weeks)	4·0 (2 to 7)	7·0 (2 to 23)	0·025
No of symptomatic respiratory illnesses during study	10·0 (6 to 12)	6·5 (4 to 8)	0·005
No of episodes of bronchopulmonary obstruction during study	9·0 (6 to 12)	4·5 (3 to 6)	<0·005
Total obstructive score	19·5 (12 to 23)	12·0 (7 to 22)	0·025
Mean obstructive score an episode	5·5 (5 to 6·6)	5·3 (4 to 7)	0·36
Duration of treatment with β-2 agonists (weeks)	20·0 (12 to 30)	7·0 (3 to 12)	<0·005
Duration of treatment with theophylline (weeks)	8·5 (6 to 14)	2·0 (1 to 8)	<0·005
Total IgE (kU/l) at end of study	11 (4 to 94)	15·5 (5 to 41)	0·49

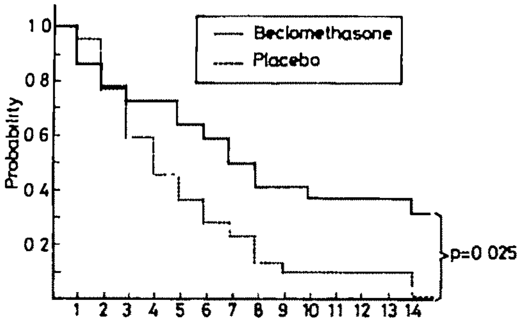

Fig 1 *The probability of not contracting an acute symptomatic respiratory tract illness as a function of time in weeks after start of treatment with placebo and with nebulised beclomethasone dipropionate calculated by the Kaplan-Meier estimate and Gehan's statistic*

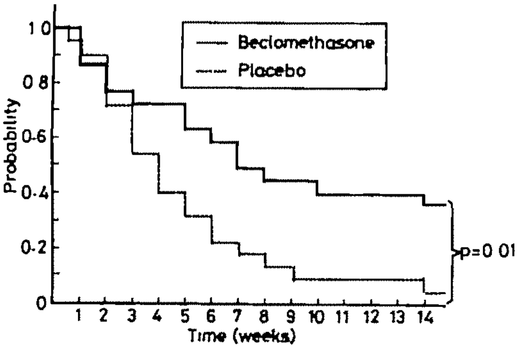

Fig 2 *The probability of not contracting an episode of bronchopulmonary obstruction as a function of time in weeks after start of treatment with placebo and with nebulised beclomethasone dipropionate. Calculated by the Kaplan-Meier estimate and Gehan's statistic.*

nebulised beclomethasone dipropionate and placebo during the first eight weeks of the study period, other symptomatic treatment was given as necessary according to the clinical condition, and recorded. The placebo group were treated with β_2 agonists (usually by inhalation) for significantly longer periods of time than the beclomethasone dipropionate group (table 3). The same was found for theophylline (usually given rectally or orally) (table 3).

Total IgE did not differ between the two groups at the end of the study (table 3). Six children in the placebo group and one child in the beclomethasone dipropionate group had positive RASTs at the end of the study, whereas four children in the placebo group and one child in the beclomethasone dipropionate group had positive skin tests at the end of the study. These differences were not significant.

Discussion

The association between bronchiolitis in infancy and subsequent obstructive airways disease[1 2] may be a result of increased bronchial hyper-reactivity as Henry *et al*[11] found two years after acute broncholitis. The prophylactic effect of inhaled beclomethasone dipropionate as powder or aerosol for childhood asthma[3 4] may possibly work through inhibition of the enzyme phospholipase A_2, preventing the release of prostaglandins and leukotrienes.[12]

In the present study the positive effect of nebulised beclomethasone dipropionate was already apparent after the first week of treatment. This effect increased gradually throughout the period, and also after the eight week treatment. Several observations confirm the beneficial effect of nebulised beclomethasone dipropionate: time until the first symptomatic respiratory illness and obstructive episode after starting treatment, number of symptomatic respiratory illnesses and episodes of bronchopulmonary obstruction during the entire year of follow up, total obstructive score during the study period, and a reduction in the use of other treatments in the beclomethasone dipropionate group. The confidence intervals of the time until the first episode of bronchopulmonary obstruction (table 3) confirm the prolonged effect after stopping treatment. It is of interest that the number of diagnosed respiratory virus infections did not differ between the two groups, whereas the number of symptomatic respiratory illnesses and episodes of bronchopulmonary obstruction were less in the beclomethasone dipropionate group. This suggests that nebulised beclomethasone dipropionate may indirectly reduce bronchial hyper-reactivity

The two treatment groups had been carefully matched and were comparable. The placebo group was slightly though not significantly older than the beclomethasone dipropionate group at the time of entry in the study, which probably accounts for the difference in weight. No other significant differences in background variables were found.

Other authors have reported similar results, though in different groups of patients Maayan *et al*[13] showed improvement of lung function and symptomatic score after two weeks treatment with nebulised beclomethasone dipropionate in nine infants aged 15 to 36 weeks old who had persistent wheezing after acute bronchiolitis. Their study was double blind with few patients, had no follow-up, and also had the possibility of a carry over effect because of the crossover design.[13] Both their study and the present study raise the possibility that inhalation with nebulised beclomethasone dipropionate at the time of recurrent respiratory infections with bronchopulmonary obstruction may have a prolonged subsequent effect after treatment has finished. This may be caused by the anti-inflammatory effect of the inhaled steroid.

Pedersen and Prahl[14] treated 13 children with bronchial asthma aged two to 26 months with nebulised beclomethasone dipropionate in an open study without placebo. They found that 15 of the 18 children improved during the treatment period of two to six months.

Storr *et al*[15] evaluated the use of nebulised beclomethasone dipropionate over a six month period in 29 children with bronchial asthma aged 20 months to 5·6 years old in a placebo controlled double blind study. They found that nebulised beclomethasone dipropionate was significantly better than placebo, whereas Webb *et al*[16] in a placebo controlled double blind crossover study of 16 children with moderate to severe asthma, age range 18 months to six years, only found a favourable trend with nebulised beclomethasone dipropionate which was not significant. In the study of Webb *et al*, however, only 13 of 16 children completed the study. The two treatment periods, each consisting of two months of active or placebo treatment, did not have any washout period in between.[16] Although the patients in the present study were younger and in a different category from those of Storr *et al*[15] and Webb *et al*,[16] our results may partly explain the differences between these two studies. We found that nebulised beclomethasone dipropionate was effective even after stopping treatment, thereby increasing the likelihood of a carry over effect in a crossover study. This makes the interpretation of data generated in crossover studies difficult.[16]

The evidence at present supports the prophylactic effect of nebulised beclomethasone dipropionate in obstructive airways disease in infants and small children. We have shown in a previous study[2] that infants at particular risk of recurrent obstructive episodes after acute bronchiolitis may be identified by a discriminant function analysis at the time of the acute attack. Infants identified in this way may benefit from nebulised beclomethasone dipropionate. The present study suggests that inhalation of nebulised beclomethasone dipropionate at a critical time period for infants and children at risk may have a prolonged effect (after treatment has been stopped) on the subsequent development of recurrent episodes of bronchopulmonary obstruction and hence upon the possible development of asthma in these children. These suggestions must be confirmed by further studies. Treatment of this kind may be of great value, especially as inhalation of topical steroids in moderate doses is devoid of serious side effects during prolonged periods of treatment.[3]

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IgG subclass deficiency in asthma

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SUMMARY Total immunoglobulin G (IgG) and subclasses were measured in serum samples from 82 children with chronic asthma, aged 1·5 to 6·3 years, and 76 controls. Concentrations of IgG_1, IgG_2, IgG_3, and total IgG were significantly lower in asthmatic children aged 1 to 5, and IgG_2 concentrations were also significantly lower in asthmatic children over 5 years of age. Twenty eight asthmatic children had at least one value in the deficient range, and 26 had IgG_2 deficiency alone or in combination. Five children had IgG_2 and IgA deficiency. These 28 children were significantly younger and fewer had raised IgE concentrations than the remainder.

IgG subclass deficiency, which may reflect delayed maturation of the immune system, is common in young asthmatic children and may have a role in the pathogenesis of the disease.

The importance of respiratory infection in precipitating attacks of asthma is well known. Deficiencies of IgG limited to one or more subclasses have been recognised in children with recurrent infections[1] and one small study found evidence of IgG subclass deficiency in 'non-allergic children with chronic chest symptoms'.[2] Because other forms of immunodeficiency have been associated with atopic diseases, we decided to study IgG subclass concentrations in a large group of chronic asthmatic children.

Patients and methods

We studied 82 children with chronic asthma, all of whom were attending the paediatric respiratory clinic at King's College Hospital. Children were included if they had asthma severe enough to warrant regular bronchodilators or prophylactic medication—that is, at least one severe attack a month, or symptoms on most days. Fifty six boys and 26 girls aged 1·5 to 6·3 years were recruited. The first symptoms of asthma occurred under the age of 1 year in 36, and under the age of 2 in 69. Half the children had symptoms of rhinitis, and half had present or past symptoms of eczema. Skin testing to six common allergens was carried out on 69, and yielded one or more positive reactions in 55. Sixty six had raised serum IgE concentrations (more than two standard deviations above the age matched mean). Forty eight children required steroids by inhalation, five sodium cromoglycate, 10 theophylline, and 19 regular β agonists. Serum samples from 76 unselected healthy controls, 38 boys and 38 girls aged 1 to 6·8 years were also analysed. These children were recruited in conjunction with the Michael McGough Foundation; they were in good health at the time of the study and had no history of serious disease.

We compared values for male and female controls to determine whether there was any sex difference in IgG subclass concentrations. Because concentrations of IgG subclasses vary with age,[3] asthmatic and control children were divided in three groups 1 to 2·99 years, 3 to 4·99 years, 5 to 6·99 years, for the purposes of analysis so that age matched comparison could be carried out. In the 1–2·99 years age group there were 17 controls (eight of whom were boys) and 22 asthmatic children (15 of whom were boys); in the 3–4·99 years age group there were 22 controls (11 of whom were boys) and 42 asthmatic children (31 of whom were boys); and in the 5–6·99 years age group there were 37 controls (20 of whom were boys) and 18 asthmatic children (10 of whom were boys). In both asthmatic and control groups were calculated the geometric mean and ranges using logarithmic transformation of the data.[4] The significance of differences between values in control and asthmatic children were assessed using Student's *t* test and the Wilcoxon rank sum test, probabilities of less than 0·05 being accepted as significant.

Asthmatic children with abnormal concentrations of IgG subclasses were compared with the remainder for age, and clinical and atopic state. The χ^2 test was used to assess the significance of any differences.

IgG subclasses were measured using an enzyme linked immunosorbent assay (ELISA) based on the method described by Aucouturier *et al.*[5] The monoclonal antibodies used were: IgG$_1$, clone NL16 (WHO/IUIS HP 6012) diluted 1/100; IgG$_2$, a mixture of clone GOM2 (HP 6009) and HP 6014, diluted 1/100; IgG$_3$, clone ZG4 (HP 6010) diluted 1/1000; and IgG$_4$, clone RJ4 (HP 6011) diluted 1/100. All monoclonal antibodies were obtained from Oxoid (Bedford, UK).

Microtitre plates were coated with purified monoclonal antibody of the relevant subclass at optimal dilution, in 0·01 mol/l phosphate buffer, 0·15 mol/l in sodium chloride, pH 7·4 (phosphate buffered saline) overnight at 4°C. Assays were conducted in triplicate in a volume of 100 µl in wells of polystyrene microtitre plates (Dynatech Immulon M129B, Dynatech Laboratories Ltd, Sussex, UK). After discarding the coating solution the wells were incubated with 5% bovine serum albumin in phosphate buffered saline, for one hour at 37°C to block residual reactive sites on the plastic wells. The plates were then washed with casein trometamol (Tris) buffer (0·05% casein, 0·9% sodium chloride, 0·01% thimersol, 10 nmol/l Tris hydrochloric acid, pH 7·6). All washes were done with an automated plate washer (Dyantech Autowash 2000). Patient or control serum was added at a dilution of 1/40 in phosphate buffered saline containing 1% bovine serum albumin and incubated for two hours at 37°C. A standard curve was established for each subclass using a reference serum preparation SPS-01 (Royal Hallamshire Hospital, Sheffield). After a further wash with casein Tris buffer, a peroxidase conjugated goat antihuman IgG antibody (Tago Inc) diluted 1/1000 in phosphate buffered saline was added and incubated for 1·5 hours at 37°C. After a final wash with phosphate buffered saline, the peroxidase activity of each well was determined with the colorimetric substrate, O-Phenylenediamine (0·4 mg/ml) and the reaction stopped with 2 mol/l sulphuric acid. The absorbance of the wells was determined at 490 nm using a Dynatech MR700 Elisa reader.

Each serum sample was studied at least twice, and a sample from a normal serum pool was included in every plate. The intra-assay coefficient of variation was 8% and the interassay coefficient of variation was 14%. A good correlation between the concentrations of IgG obtained by summing subclasses and total IgG concentrations was found on measurement by laser nephelometry (linear regression analysis r=0·89).

Informed consent was obtained from all parents and the study was approved by the hospital ethical committee.

Table 1 *Mean (range) IgG concentrations (g/l) in the three age groupings*

	Control children	*Asthmatic children*	*t*	*p Value*
Age 1 to 2·99 years:				
Total IgG	10·04 (7·4–13·7)	7·8 (5·0–12·2)	4·16	<0·01
G$_1$	6·6 (4·0–10·8)	5·5 (3·4–8·7)	2·52	<0·05
G$_2$	2·1 (1·6–2·8)	1·3 (0·4–3·9)	3·53	<0·01
G$_3$	0·89 (0·4–1·9)	0·73 (0·4–1·3)		NS
G$_4$	0·3 (0·1–0·5)	0·2 (0·1–0·4)		NS
Age 3 to 4·99 years				
Total IgG	9·9 (6·6–14·9)	8·1 (5·6–11·5)	4·26	<0·01
G$_1$	6·4 (4·2–9·9)	5·5 (3·7–8·2)	2·74	<0·01
G$_2$	2·3 (1·2–4·3)	1·5 (0·8–3·1)	3·91	<0·01
G$_3$	0·84 (0·42–1·7)	0·69 (0·42–1·13)	2·63	<0·05
G$_4$	0·2 (0·1–0·8)	0·2 (0·1–0·4)		NS
Age 5 to 6·99 years				
Total IgG	9·7 (6·7–14·1)	9·05 (6·7–12·2)		NS
G$_1$	6·0 (3·8–9·6)	6·27 (4·5–8·8)		NS
G$_2$	2·5 (1·3–4·8)	1·72 (1·0–3·1)	3·87	<0·01
G$_3$	0·76 (0·33–1·74)	0·73 (0·4–1·35)		NS
G$_4$	0·2 (0·03–1·7)	0·2 (0·1–0·4)		NS

Results

Values for boys and girls in the control group were similar for all subclasses and for total IgG.

Concentrations of IgG$_1$, IgG$_2$, IgG$_3$ and total IgG were lower in asthmatic children aged 1 to 2·99 and 3 to 4·99 years when compared with age matched controls. IgG$_2$ values were also lower in asthmatics aged 5 to 6·99 years ($p<0·05$) (table 1, figure).

Twenty eight asthmatic children had one or more values more than two standard deviations below the mean for age matched controls. Twenty six had IgG$_2$ deficiency—alone in 13, and combined with total IgG deficiency in nine, IgG$_1$ and total in two, IgG$_3$ in one, and IgG$_3$ and total in one. One child had a low concentration of IgG with subclass concentrations within the normal ranges, and a further child had IgG and IgG$_1$ deficiency.

These 28 children with deficiencies, when compared with the remainder of the asthmatic group, were significantly younger and fewer had high IgE concentrations than the remainder. There were no significant differences in sex, age of onset, concomitant atopic disease, requirement for inhaled steroids, or skin test reactivity. Five children, all of whom had IgG$_2$ deficiency, also had IgA deficiency (table 2).

Discussion

Our results indicate that IgG subclass deficiency, predominantly IgG$_2$, is present in over one third of children under 7 with serious asthma. Five children

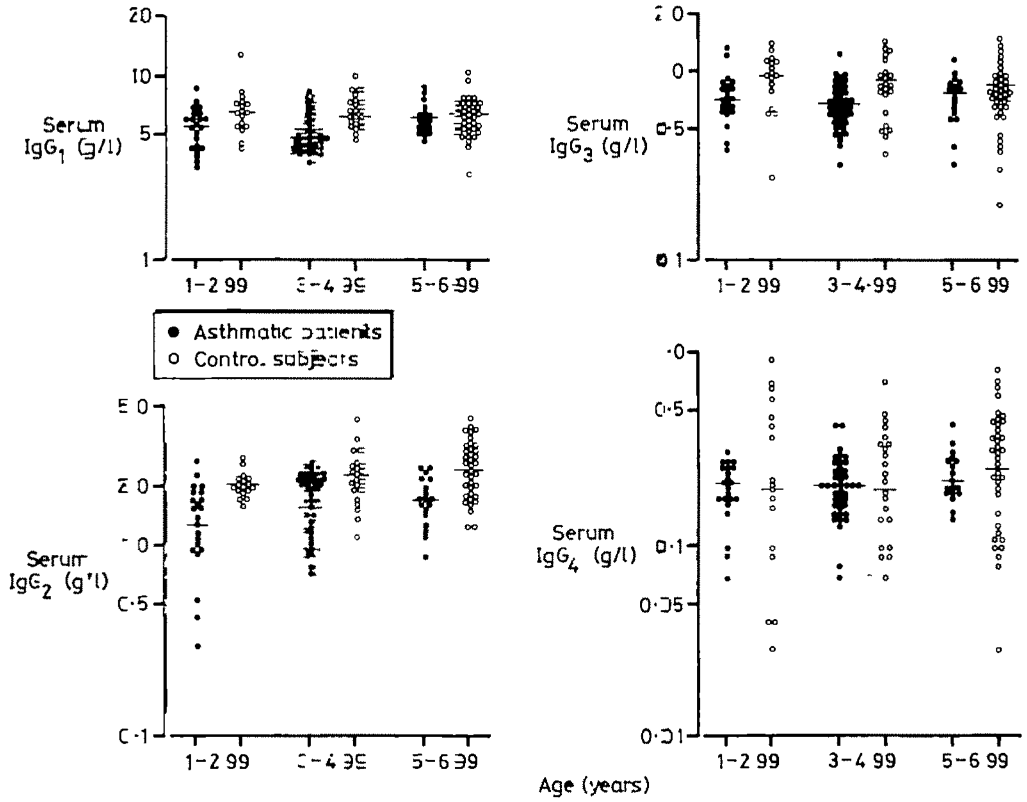

Figure *Individual values for IgG subclasses in asthmatic and control patients. The mean of each group is indicated.*

Table 2 *Comparison of asthmatics with at least one deficiency of IgG or subclass and the rest of the study group*

	Those with at least one deficiency (n=28)	*p Value*	*Those with no deficiencies (n=54)*
Mean (SD) age (months)	36·4 (15·4)	<0·05	47·8 (SD 14·9)
No (%) of boys	22 (79)	NS	34 (63)
Age at onset:			
No (%) under the age of 1 year	12 (43)	NS	24 (44)
No (%) between 1 and 2 years	10 (36)	NS	23 (43)
No (%) receiving treatment with inhaled steroids	16 (57)	NS	22 (40)
No (%) with rhinitis	15 (54)	NS	32 (59)
No (%) with eczema	13 (46)	NS	25 (46)
No (%) with positive skin tests	17/24 (71)	NS	38/45 (85)
No (%) with raised IgE concentration	17 (61)	<0·05	49 (91)
No (%) with IgA deficiency	5 (18)	NS	0

had abnormally low concentrations of IgA, and they all had concomitant IgG_2 deficiency. Total IgG deficiency has been reported in children taking oral steroids[6]; none of our children were taking oral steroids when studied, though many had received short courses previously. Multiple IgG subclass deficiency was present only in younger patients.

In the previous study of IgG subclasses in children with asthma, IgG_2 deficiency was noted in 10 of 37 'non-allergic children with chronic chest symptoms'; these children had negative skin tests and normal IgE concentrations.[2] In our study negative skin tests and normal concentrations of IgE were more common in children with deficiencies. These children were significantly younger, however, and because the incidence of positive skin tests increases with age,[7] the apparent association of G subclass deficiency and 'non-allergic' asthma may only be a reflection of a younger age group.

Atopic diseases including asthma have been linked with IgA deficiency,[8] defective yeast opsonising activity,[9] C2 deficiency,[10] and now IgG subclass deficiency. No specific immunodeficiency is accepted as predisposing to childhood asthma but the association with a variety of abnormalities indicates that some form of dysregulation of immunity may be concerned in the pathogenesis. It has been suggested that defects of the immune system that affect exclusion or elimination of antigen could be relevant in early infancy at the time of first presentation of antigen to cells making IgE[11]; clearance of adsorbed antigen might be impaired in IgG subclass deficiency.

The IgG antibody response to bacterial polysaccharide antigen resides mainly within IgG_2 subclass[12] and the antibody response to some viruses may also be restricted to a particular subclass.[13] Inability to mount an adequate IgG response might provoke or exacerbate asthma in certain children. Respiratory infection, particularly when viral, results in an increase in bronchial reactivity.[14] Perhaps protracted infection and epithelial damage enhances this effect on airway function.

Our results show that IgG subclass concentrations are significantly reduced in young asthmatics. The hypothesis that IgG subclass deficiency predisposes to asthma depends on showing that the abnormalities predate the disease. We cannot be sure that the observed deficiencies were not a consequence of asthma or its treatment, but multiple deficiencies were present only in the younger children. This suggests some type of delayed maturation and tends to favour the concept that these deficiencies are primary.

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Screening for cystic fibrosis: a four year regional experience

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SUMMARY A four year regional screening programme to detect cystic fibrosis using measurement of immunoreactive trypsinogen is described. During this period 60 infants were diagnosed; 34 by screening, 12 born with meconium ileus, and 14 not identified by the screening assay but who presented with clinical symptoms at a later age, giving an incidence of cystic fibrosis in the region during this time of 1/1807. Screening has resulted in earlier detection of cystic fibrosis in many infants, thus allowing treatment to be instituted at an early age, and genetic counselling offered to the parents. There were a number of false positives and false negatives with the immunoreactive trypsinogen screening assay. In addition, eight infants who were sweat tested at an early age had a sweat sodium concentration of <70 mmol/l, although they were subsequently shown to have cystic fibrosis. These results confirm other published data showing that sweat sodium results may be low in very young infants with cystic fibrosis. At the time of diagnosis seven (20%) of the infants identified by screening were totally asymptomatic and several additional children had symptoms of such a type that the diagnosis of cystic fibrosis had not been considered at the time of screening. Despite the problems experienced it has been decided to continue screening.

It has been reported that immunoreactive trypsinogen concentrations were raised in blood in infants with cystic fibrosis.[1] A number of subsequent trials have shown that immunoreactive trypsinogen could be estimated on dried blood spots as a screening assay for cystic fibrosis in the new born period.[2 3] These reports showed encouraging results, and thus it was decided that it would be useful to assess the ability of this assay to detect cystic fibrosis in conjunction with the existing screening programme for phenylketonuria and congenital hypothyroidism in Northern Ireland.

Methods

Blood specimens, obtained by heel prick and collected on to filter paper cards, were taken between 5 and 8 days of age from all infants born in Northern Ireland. Before August 1983 these samples were used to screen for phenylketonuria and congenital hypothyroidism. Since August 1983 measurement of immunoreactive trypsinogen has been included as a screening test for cystic fibrosis. A second heel prick sample was obtained from all infants whose initial trypsinogen value was high, usually at 3–4 weeks of age. If the repeat trypsinogen concentration was also high the baby was seen by a paediatrician with experience in management of cystic fibrosis, and a full clinical examination and sweat test carried out; the child was usually 4–6 weeks old at this time.

Measurement of immunoreactive trypsinogen, on blood spot specimens, was carried out using the CIS Neonatal Trypsin Radioimmunoassay (CIS (UK) Ltd). The within assay coefficients of variation for the three concentrations of immunoreactive trypsinogen, 24, 55, and 108 µg/l, were 8·5%, 6·1%, and 5·2% respectively. The between assay coefficients of variation at the same concentrations were 9·3%, 8·3% and 7·7%, respectively. From a precision profile for the assay the range for which the between assay coefficient of variation is <10% has been shown to be 10–140 µg/l. To establish a reference range for the assay immunoreactive trypsinogen measurements were carried out on 4000 infants born during June and July 1983. These results were not included in the four year period of assessment of the assay and one infant born during June and July

1983 was subsequently shown to have cystic fibrosis. A frequency distribution of immunoreactive trypsinogen results on these 4000 infants is shown in fig 1. The value at the 95th centile is 80 µg/l and at the 98th centile is 120 µg/l.

During the first year of blood trypsinogen screening in Northern Ireland the 98th centile was used as the cut off level. Thus a second sample was requested on any infant whose initial screening result exceeded 120 µg/l. If the trypsinogen value for the repeat sample was also greater than 120 µg/l the child was referred for a sweat test and a clinical examination. After one year of screening, using this cut off value, four false negatives had been identified, and in three of these the results were between the 95th and the 98th centile for the assay. For this reason, it was decided to alter the cut off value to the 95th centile (80 µg/l), and this value has been used as the cut off since August 1984.

Sweat tests were carried out using the method of Gibson and Cooke.[4] A sweat sodium concentration of greater than 70 mmol/l was considered to be suggestive of cystic fibrosis in the neonate. In infants with equivocal sweat sodium results—40–70 mmol/l —the sweat test was repeated. A diagnosis of cystic fibrosis was not made until three tests with sweat sodium concentrations >70 mmol/l were obtained. Since 1985 the sweat chloride concentration has also been measured and a concentration of >70 mmol/l considered to be commensurate with a diagnosis of cystic fibrosis. The sweat chloride is often greater than the sweat sodium concentration in cystic fibrosis, and the sum of the sweat sodium and sweat chloride concentrations greater than 140 mmol/l.

Results

IMMUNOREACTIVE TRYPSINOGEN CONCENTRATIONS

During the four year period 108 424 infants were screened, and a second specimen was requested from 5120 (5%) in whom the initial trypsinogen result was greater than the cut off level. A second raised trypsinogen concentration was measured in 136 of these repeats, and 34 were identified as having cystic fibrosis after clinical examination and sweat testing. One hundred and two false positives had a normal sweat test and no other indication to suggest a diagnosis of cystic fibrosis, although two raised trypsinogen concentrations had been measured. Fourteen children subsequently were diagnosed as having cystic fibrosis, although they did not have raised concentrations of trypsinogen on screening. Of these false negatives, three infants born in the first year of screening had results between the 95th and 98th centile. In two other babies an initial raised trypsinogen result was followed by a low concentration on repeat testing, and in the rest of those with a false negative result at no time was the concentration of trypsinogen raised.

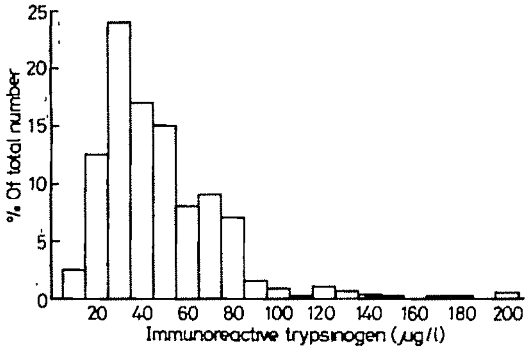

Fig 1 *Frequency distribution of blood immunoreactive trypsinogen results in 4000 infants, taken consecutively*

A total of 12 infants presented with meconium ileus. Two of the 12 infants had raised trypsinogen concentrations and would have been identified by the screening programme; the remainder all had low trypsinogen concentrations. It is our policy, however, to carry out a sweat test on all infants with meconium ileus thus identifying those with cystic fibrosis.

The range of immunoreactive trypsinogen concentrations for 34 true positive and 102 false positive results are shown in fig 2. The trypsinogen concentrations in both of these groups range from 80–>200 µg/l. The median values for the true positive groups are 200 µg/l for the initial screening result, and 146 µg/l for the repeat test; in the false positive group the median values for the two tests are 110 µg/l and 122 µg/l respectively. On the basis of trypsinogen testing there was no way to separate the false positive results from those that were later shown to be associated with cystic fibrosis on the basis of sweat testing.

SWEAT TEST

A sweat test was carried out on all infants with two raised immunoreactive trypsinogen results. The mean sweat sodium concentration at diagnosis for infants with cystic fibrosis was 92 mmol/l, with a range of values from 70 to 135 mmol/l. The corresponding values for the false positive group were 18 mmol/l and 9–33 mmol/l In 27 infants with cystic fibrosis, who also had a sweat chloride measurement, 25 had a sweat chloride concentration in excess of the sweat sodium concentration, and in 24 of these 27 infants the sum of the sodium and chloride concentrations was greater than 140 mmol/l.

Seven infants with high trypsinogen values, who

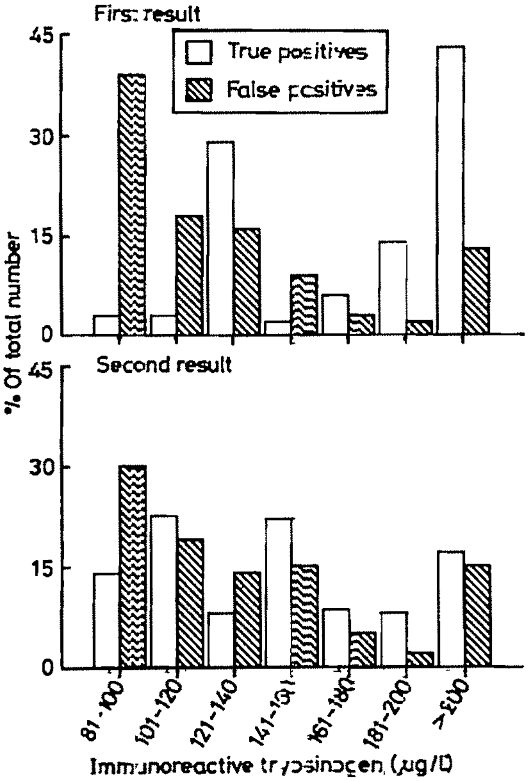

Fig 2 *Distribution of blood immunoreactive trypsinogen results in 136 infants who had high (>95th centile) concentrations on two occasions. Thirty four infants were subsequently shown to have cystic fibrosis (true positives).*

were shown to have cystic fibrosis, had a sweat sodium concentration in the range 40–70 mmol/l on their initial sweat test, and a further infant had an initial sweat sodium concentration of 15 mmol/l. In each of these children the sweat test was repeated either because of strong clinical indications of cystic fibrosis, or because there was a family history of cystic fibrosis, and eventually a diagnosis of cystic fibrosis was supported by three sweat sodium estimations of >70 mmol/l.

When an infant was diagnosed as suffering from cystic fibrosis, all other siblings were sweat tested. In 1984, after diagnosis of cystic fibrosis in a 6 week old girl after positive screening results, three older children of the family were sweat tested. Two of these had positive sweat tests and were diagnosed as having cystic fibrosis. Their ages were 3 years and 5 years. The older child had been treated for rectal prolapse at the age of 2 years, but the possible diagnosis of cystic fibrosis had not been considered.

CLINICAL ASSESSMENT

Most of the infants shown to have cystic fibrosis as a result of the screening programme already had signs or symptoms, or both, of cystic fibrosis as shown in table 1. In the four year screening period seven infants (20% of those subsequently shown to have cystic fibrosis) were totally asymptomatic at the time of diagnosis. Three children had severe chest infections and the diagnosis of cystic fibrosis had been suspected before the immunoreactive trypsinogen results were known. In 24 children, however, the diagnosis had not been suspected until the screening results became available. When examined by the paediatricians involved in this study, 12 were found to have a history of mild chest infection, 13 to have persistent diarrhoea, and an additional five had no obvious symptoms suggestive of cystic fibrosis, although they were underweight for their age.

Table 2 shows that of those children with cystic fibrosis and low immunoreactive trypsinogen values on screening, only three in the four year period were asymptomatic; these children were investigated after the diagnosis of cystic fibrosis in siblings. The remainder had pronounced symptoms, the most important feature being failure to thrive, attributed in four cases to repeated pulmonary infections and to persistent diarrhoea in the remainder.

EFFECT OF SCREENING ON THE AGE AT DIAGNOSIS

Table 3 shows that the median age at which the

Table 1 *No of infants with cystic fibrosis, identified by screening, and their symptoms at presentation*

Symptom	*1983/4*	*1984/5*	*1985/6*	*1986/7*
Failure to thrive	5	4	5	4
Diarrhoea	2	3	5	3
Chest infection	6	3	3	3
Asymptomatic	2	1	2	2
Total No/year	9	7	9	9

Table 2 *No of infants with cystic fibrosis, missed on screening, and their symptoms at presentation*

Symptom	*1983/4*	*1984/5*	*1985/6*	*1986/7*
Failure to thrive	2	5	2	0
Diarrhoea	2	1	1	0
Chest infection	1	4	3	0
Asymptomatic	2	0	1	0
Total No/year	4	6	4	0*

*None identified so far

Table 3 *Age at diagnosis before and after screening*

Year of birth	*Total No diagnosed*	*No missed on screening*	*No with meconium ileus*	*Median age at diagnosis (range)*
		Not screened		
1980/1	12	—	2	6·8 months (6 weeks–7 years)
1981/2	13	—	2	4·5 months (4 weeks–4 years)
1982/3	14	—	1	9·5 months (4 weeks–4·5 years)
		Screened		
1983/4	15	4	2	6 weeks (4 weeks–2·5 years)
1984/5	14	6	1	6 weeks (4 weeks–23 months)
1985/6	15	4	2	6 weeks (4 weeks–14 months)
1986/7	16	0*	7	4 weeks (4 weeks–8 weeks)

*None identified so far

diagnosis of cystic fibrosis was made, since screening was commenced in August 1983, was six weeks, with a median age for infants born since August 1986 of 4 weeks; this was due to the large number who had meconium ileus in that year. Fourteen infants not identified by screening were diagnosed at a later date, the oldest being 2·5 years. In the three years before screening, the median ages for diagnosis of cystic fibrosis were 6·8 months, 4·5 months, and 9·5 months, and of children born in those years, the oldest age at which a diagnosis of cystic fibrosis was made was 7 years.

DIAGNOSTIC VALUE OF THE SCREENING TEST

On the basis of the screening results the sensitivity of the test was calculated as 60%, the specificity 99·9%, the predictive value of a positive result 34%, and the predictive value of a negative result 99·9%. The sensitivity of the test was improved to 73% if this figure was calculated having excluded negative results in infants born with meconium ileus. The known incidence of cystic fibrosis in Northern Ireland during this four year period was 1/1807.

Discussion

All infants born in Northern Ireland during the past four years have had immunoreactive trypsinogen concentrations measured on dried blood spot specimens. These samples were taken at the same time as those used in the screening procedure for phenylketonuria and congenital hypothyroidism. As a result of screening there has been a significant reduction in the age at which the diagnosis of cystic fibrosis is made. Furthermore, 20% of infants were judged to be totally asymptomatic at the time of diagnosis, and a further 17% had mild to moderate generalised symptoms not thought to be pathognomonic of cystic fibrosis At the time of diagnosis these children were about 6 weeks of age, and most did develop specific symptoms at a later stage.

The region of Northern Ireland is a small one, with an annual birth rate of about 28 000, and there is not a great deal of population movement in and out of the region. There is one single large referral unit in Belfast for patients with cystic fibrosis On account of these factors very few patients are lost to follow up, and this may contribute to the fact that in this paper we describe a higher incidence of false negative results than have been indicated in previous reports. Three infants who were false negatives, but with results close to our cut off value in the first year of screening, would have been detected if the lower cut off value had applied throughout the time of screening. Two further false negative results were caused by one high followed by a low trypsinogen concentration, and this may have been because of incorrect timing of the second specimens, as initially raised trypsinogen concentrations in cystic fibrosis are known to fall to within the normal range at varying rates in different infants.[3] In the remaining nine false negatives the results of screening were well within the normal limits, and no explanation could be put forward to suggest why the results were low in infants with cystic fibrosis. Of 12 infants born with meconium ileus, 10 had low results on screening, a finding which has been reported in a number of studies.[3,5] As children born with meconium ileus should be investigated for cystic fibrosis their low results on screening should not cause a serious diagnostic problem, although it is important to emphasise the relationship between meconium ileus and low concentrations of immunoreactive trypsinogen.

The number of repeat specimens requested during this period of screening was very high. A second specimen is obtained on all infants with results greater than the 95th centile for the assay; other centres quote much lower numbers of second specimens.[3 6] In addition, the false positive rate for the screening assay was very high, with a false positive being defined as those having two raised immunoreactive trypsinogen results, but a normal sweat test, and no clinical signs of cystic fibrosis. Although the median trypsinogen result for the second specimen showed a tendency to be lower for false positives compared with those infants who did have cystic fibrosis, there was no clear cut difference between the groups.

It is widely recognised that definitive sweat test results are not always easy to obtain.[7 8] In this context it is often recommended that sweat tests should be carried out by fully trained personnel, using a well defined protocol[4] in the sweat tests carried out as a result of our screening programme we have found these factors to be important. A recent report describes sweat tests in young infants with an ultimate diagnosis of cystic fibrosis, but with sweat sodium concentrations below 60 mmol/l at the time of the first sweat test.[9] Eight children with raised trypsinogen concentrations in our screening programme had a sweat sodium that was not sufficiently high at 6 weeks of age to confirm cystic fibrosis. In seven of these children equivocal sweat test results were obtained on a number of occasions, but in one child with an initial sweat sodium concentration of 15 mmol/l no further sweat tests were carried out until the child was 2·5 years old. Each of these children has subsequently been identified as having cystic fibrosis on the basis of clinical data, family history, trypsinogen results, and eventually all have been shown to have abnormal sweat electrolytes on three separate occasions.

These results serve to indicate that especially in young children the sweat test cannot always be considered to be reliable, and a diagnosis of cystic fibrosis should be considered if the clinical findings point to this, even in the presence of equivocal or normal sweat electrolyte concentrations. In addition, we have found it necessary to establish appropriate reference ranges for sweat sodium and chloride concentrations in the population of young infants requiring sweat tests as a result of positive trypsinogen screening values.

From the description of symptoms seen in those children identified by screening as having cystic fibrosis, it can be appreciated that 20% were truly asymptomatic when diagnosed at this early age. An interesting feature was the number of infants presenting at 6 weeks with failure to thrive or inadequate weight gain. In most cases this was due to the infant having diarrhoea In some cases the parents, particularly those of first born children, did not realise that the child was having frequent bowel movements; they accepted their child as being normal. Health professionals concerned with advising parents should be aware of the possibility of cystic fibrosis in an infant with mild diarrhoea or inadequate weight gain. In several cases the parents had been advised that their child was allergic to milk products, although they were eventually shown to have cystic fibrosis.

From the results in table 3 it can be seen that the median age at diagnosis for the screened population is less than that for children born in the three years before screening. It is possible that additional false negative cases will be identified in the future. It should be noted, however, that in the last seven years the number of children in Northern Ireland shown to have cystic fibrosis has remained reasonably constant, with 13–16 children being diagnosed each year In addition, the overall known incidence of cystic fibrosis in Northern Ireland during the last four years is 1/1807, which is a high incidence, making it unlikely that there are many more unidentified infants with cystic fibrosis born during this period of time.

In conclusion, this screening programme has resulted in a lowering in the median age at which the diagnosis of cystic fibrosis is made and a considerable reduction in the anxiety of parents with an undiagnosed sick child. It is also possible to offer genetic counselling to these parents. It must be recognised that in our hands immunoreactive trypsinogen has not proved to be an ideal screening test for cystic fibrosis. The clinicians involved in the study, however, feel that because of the earlier age at diagnosis in a large number of infants with cystic fibrosis the screen should continue for a further period of time. It seems likely that other tests that closely reflect the underlying genetic or metabolic abnormalities will soon become available.

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Two minute walking distance in cystic fibrosis

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SUMMARY We have evaluated the 'two minute walking distance' in children with cystic fibrosis as an objective measurement of exercise tolerance. There was a strong correlation between walking distance and height in 89 normal children (r=0·72). Fifty children with cystic fibrosis showed a similar correlation (r=0·56) with a mean result of 94% of that expected for height compared with the normal children. There was a training effect in the normal children with the second walk being significantly better than the first, but this was not evident in children with cystic fibrosis. The test was reproducible with no significant change in 12 children retested after one to three months. Sixteen children with cystic fibrosis admitted for treatment of chest disease showed a significant improvement in walking distance with treatment. Children as young as 5 years old can perform a walking distance test. It seems to be an objective way of assessing exercise tolerance and can help in evaluating response to treatment.

It is often difficult to show objective improvement in the clinical condition of patients during inpatient treatment for exacerbations of chest disease in cystic fibrosis. This has become more of a problem with the development of an increasingly aggressive approach to management that necessitates the admission of children with pulmonary function closer to the normal range. Redding *et al*[1] did show significant improvement in various measures of pulmonary function during inpatient treatment. These, however, were in children who clearly had poor lung function; peak expiratory flow rate (PEFR) was 30% of expected at admission, compared with 66% of that expected in the children admitted in our study. Cerny *et al*[2] also reported improvement in lung function during periods in hospital and additionally looked at exercise tolerance. They used an exercise test on a cycle ergometer, however, and the patients were mainly teenagers and young adults. Such studies are often not possible with younger children, even if the equipment is available, and it is another consequence of more aggressive management that younger children require admission. Apart from a simple PEFR it is difficult for them to cooperate with lung function studies, let alone complicated exercise tests.

Although easy to carry out, peak flow testing does have drawbacks in assessing response to treatment, particularly in young children. PEFR varies during the day, and also in response to treatment such as bronchodilators and physiotherapy. Over a period of several days it is often difficult to correlate PEFRs done at different times and to draw appropriate conclusions. This short term variability also means it is not particularly useful in looking at changes in lung function over a period of years. We have also become aware that some children 'cheat' with a peak flow meter, accelerating flow in the mouth with the tongue, a phenomenon also reported in older patients.[3]

This led us to look into other ways of objectively assessing improvement in children with cystic fibrosis We have assessed night time cough charts and daily sputum weights as well as simple tests of exercise tolerance. It has been shown that the 12 minute,[4] and two and six minute[5] walking distances are reproducible measurements of exercise tolerance in adult patients with chronic airways obstruction. In view of the short attention span of many young children, and the high reproducibility of the two minute walking distance,[5] we decided to evaluate this test in our young patients with cystic fibrosis.

Method

Tests were carried out in an enclosed hospital corridor with no gradient along a 35 metre course marked at five metre intervals. Each child was asked to walk as fast as they found comfortable but not to run. Simple verbal encouragement was given at each turn. Walks of two minutes were timed by stopwatch and the distance covered measured by tape from the nearest five metre mark. In view of the known training effect of exercise tests[6] two walks were performed wherever possible, with five to 10 minutes rest in between. The greater of the two distances was used for analysis. All tests were solo and therefore non-competitive. Age, height, and PEFR before and after the walk were recorded. All tests were conducted by one of two examiners (CJU or JCT).

We tested three groups of children: group 1—normal children admitted for minor operations, and the healthy siblings of inpatients; group 2—'well' children with cystic fibrosis attending for routine clinical follow-up; and group 3—children with cystic fibrosis admitted for exacerbations of their chest disease, who performed the walking test before, during, and after treatment.

Statistical analysis was by linear regression with Pearson's coefficient of correlation, and Student's paired and unpaired *t* tests.

Results

GROUP 1

Eighty nine normal children completed the test (32 girls and 57 boys, age range 5 to 16 years, mean 9½ years). The preponderance of boys is a reflection of their higher admission rate for minor operations. There was no difference between the boys and girls when results against height were compared using the *t* test ($p>0.05$). Fig 1 shows the scattergram of walking distance against height for these children with the regression line and 10th and 90th centiles. There was a strong correlation between them (Pearson correlation coefficient 0·72; $p<0.0001$) and also between walking distance and both age and PEFR ($r=0.71$ and 0·67, respectively). To look at the effect of training the first walk was compared with the second. There was a significant improvement on second testing ($p<0.01$), confirming the results of adult studies.

GROUP 2

Fifty children with cystic fibrosis took part (27 girls and 23 boys, age range 5 to 16 years, mean 11 years), and 12 of these did the test on more than one occasion. Fig 2 shows the best recorded walking distance of each individual child plotted against height, with the regression line, and 10th and 90th centiles for the normal children superimposed. There is positive correlation between walking distance and height in the children with cystic fibrosis but with greater variation (Pearson's correlation coefficient 0·56, $p<0.0001$).

Most of these children had measurements less

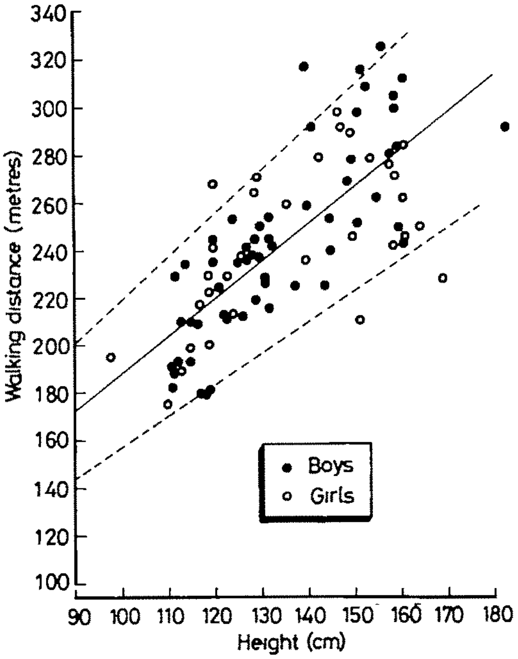

Fig 1 *Two minute walking distance plotted against height in 89 normal children (———— 50th centile, – – – – 10th and 90th centiles).*

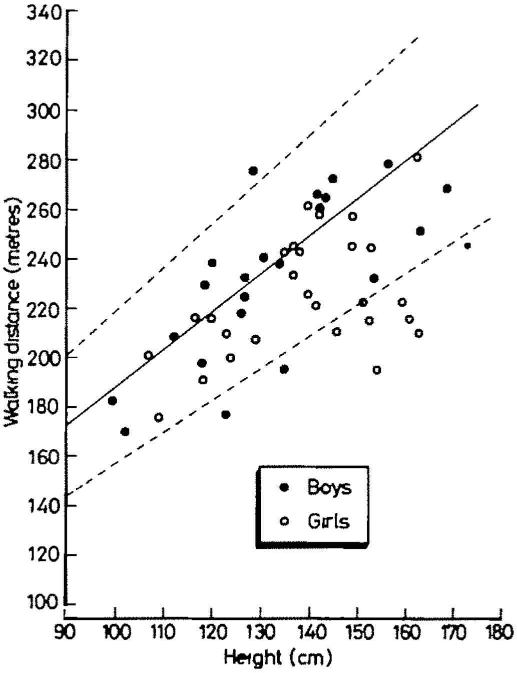

Fig 2 *Two minute walking distance plotted against height in 50 children with cystic fibrosis (———— 50th centile for normal children, – – – – 10th and 90th centiles for normal children).*

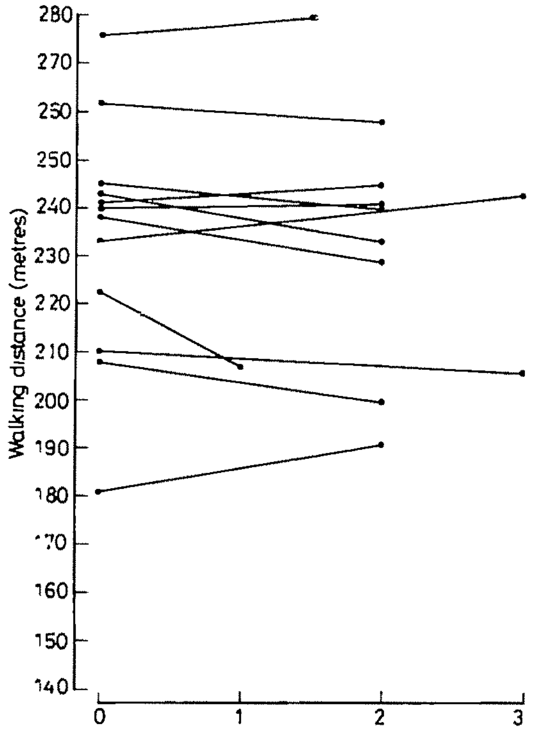

Fig 3 *Two minute walking distance plotted against time in 12 children with cystic fibrosis in stable clinical condition.*

than but close to the regression line for normal children (mean (SD) 93·7 (9·9)% that of the normal group), with 10 recorded values below the tenth centile for normal children. The differences between the normal children and those with cystic fibrosis were significant (p<0·001). Again there was positive correlation between walking distance and both age and PEFR (r=0·56 and 0·67, respectively).

First and second walks were again compared and, interestingly, there was no significant difference between the two in the children with cystic fibrosis. This seems to rule out a training effect in the children with cystic fibrosis, but to assess reproducibility of the walking distance further, 12 children with cystic fibrosis repeated the test one to three months after initial testing (seven girls and five boys, age range 5 to 15 years, mean 10 years). Their clinical condition was thought to be unchanged: mean (SD) PEFR 95·2 (22·5)% of the expected value on the first test, and 94·6 (21·6)% on subsequent testing (NS). The largest change was +15%. Changes in walking distance with time are shown in fig 3. There is little variation in each child's performance: mean (SD) values were 96·7 (12)% of expected on the first test, and 95·6 (12)% on subsequent testing (NS). The largest change was −5·9%. The mean coefficient of variation calculated from all four walks for each child over two tests was just 2·6% (range 1·9–5·9%).

GROUP 3

Sixteen children with cystic fibrosis receiving inpatient treatment performed serial walks while in hospital (9 girls and 7 boys, age range 6 to 16 years, mean 12½ years; one patient was tested twice). In addition to intensive physiotherapy, all but two of these patients were treated with intravenous antibiotics for exacerbations of chest infections caused by *Pseudomonas aeruginosa* (one received nebulised antipseudomonal antibiotics and one an oral antibiotic for infection with *Staphylococcus aureus*).

The results are shown in fig 4. There was

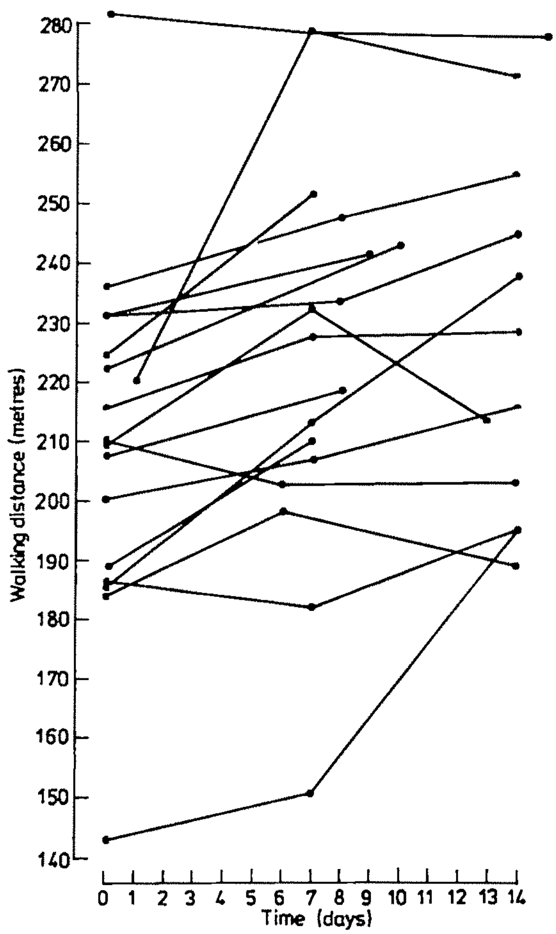

Fig 4 *Two minute walking distance plotted against time during 17 courses of inpatient treatment.*

significant improvement in the percentage of expected walking distances at the end of inpatient treatment compared with the beginning ($p<0{\cdot}005$). Mean (SD) values were 83·3 (10·9)% of expected on admission, and 90·8 (11·2)% at discharge. The largest change seen was +23·8%. These changes are significantly different from those in the untreated group ($p<0{\cdot}005$) and occur over a much shorter period of time.

The PEFR in these children was 66·1 (18·3)% of expected on admission and 80·1 (17·1)% at discharge. This change was also significant ($p<0{\cdot}005$). The largest change was +52%. Thus we have shown significant changes in both PEFR and walking distance with treatment, these differences not being present in the untreated group. PEFR showed more short term variability in both groups, as expected from the increased bronchial lability in cystic fibrosis.[7]

We were worried that the walking distance would only be discriminatory in the children with the worst respiratory function. For further analysis, therefore, the treated group were split into the fittest and the least fit eight children by PEFR and walking distance Walking distance was significantly improved after treatment in both the least fit eight children ($p<0{\cdot}05$) and the fittest eight children ($p<0{\cdot}01$). PEFR was also significantly improved with treatment in the least fit eight children ($p<0{\cdot}02$), but there was no significant difference in the fittest eight children. These results were consistent whether the group was divided by PEFR or by walking distance. This suggests that as respiratory function nears the normal range walking distance is a more discriminatory variable than PEFR, which is presumably because of the short term variability in PEFR.

Discussion

In adult patients 12 minute walking distance is a reproducible measurement that correlates with other measurements such as forced vital capacity and oxygen consumption.[4] The two and six minute tests have been shown to be equally reproducible, and correlated well with the longer test.[5] Rather than purely reflecting pulmonary function, such simple tests of exercise tolerance may give an indication of other factors important in day to day life such as motivation and endurance.[8] We feel this is an important aspect to consider when reviewing the use of such tests. Walking is an essential part of everyday life and a familiar activity to young children. By using it in an exercise test one can gain some insight into functional disability in daily living.

We found that in general children enjoyed taking part in the test—regarding it as a game—and cooperation was good even among the younger children. The fun element in the test was, we feel, an important part in gaining this cooperation. A few teenage girls were reluctant to take part and in this group we also ran into problems with unsuitable footwear; this usually resulted in a walk in bare feet or slippers. In spite of this only two children failed to complete the test, and one would not do the second walk. On two occasions children started to jog and the test was then stopped and restarted after a rest. As the tests took place in a hospital corridor there were times when it was congested, but it rarely took longer than five minutes to clear sufficiently to perform the test reliably. Children were asked to keep to one side of the corridor, both to limit lateral movement affecting the distance achieved, and to allow passage to others. The length of corridor is important, as it needs to be short enough to allow communication from one end to the other but long enough to let children get into their stride. Thirty five metres is a similar distance to that used in adult studies.[5] Encouragement was given at each turn, but not in between as this is known to affect results (at least in a six minute test).[9]

It is important to consider the effect that repeated tests have on results. Adult studies have shown an important effect of training, although there was no significant difference between second and third testing.[4] [6] For this reason we did not feel justified in asking the children to perform more than two tests at any one sitting. Our study confirms the significant effect of training between successive walks in normal children, but not in the children with cystic fibrosis. This contrasts with the adult study of McGavin *et al*[4] although they used a 12 minute walk and the tests were performed on different days, though one would expect that, if anything, this would make a training effect less likely. Another alternative is that our children with cystic fibrosis were tired from the first walk and the effect of training was therefore abolished. This is not supported by our results; there was no significant reduction in walking distance, nor was the walk sufficient to cause a significant drop in PEFR in any child, either with cystic fibrosis or normal. We were also careful to avoid testing children who were obviously tired; in practice the decision to embark on the second walk was left to the individual child, usually after a five to 10 minute rest.

The good reproducibility seen over one to three month periods in children with cystic fibrosis is further evidence that training is not having a great effect in this population. The variation seen is much smaller than that in adult studies using the 12 minute distance.[10] It has been suggested that the increased variability in the longer test implies better discrimination,[5] but no evidence for this was provided.

Although this may be true in an adult population, we feel that a longer test in children would merely create more scope for random variation and error, not to mention boredom in the children.

Ideally we would have liked to have studied the normal children over similar time periods to those used to assess reproducibility in the children with cystic fibrosis, to confirm this reproducibility. As the study was hospital based, however, and the children were undergoing minor operations, this was not feasible. In spite of this, we would agree with Butland *et al* that the evidence points to a small effect of training in the two minute walk[5] We feel the problem is largely overcome by taking the longest of two successive walks.

In view of the apparently small training effect and the good reproducibility we feel that the increase in walking distance during inpatient treatment is a true reflection of the subjective improvement of the patients. This may not be purely a result of improved lung function, but also caused by improvement in general wellbeing and morale We have also shown that this improvement is not solely in the worst affected children, and that walking distance may have an advantage over PEFR in discriminating between improvement in children with near normal lung function.

In addition to the usual measurements of lung function, we are now using the two minute walking distance to monitor changes in patients admitted with exacerbations of cystic fibrosis. We believe it gives useful objective information that may complement lung function measurements, and has the added advantage that it could be used in a district general hospital without access to a lung function laboratory. It may also supply helpful evidence in support of applications for mobility allowances.

We now intend to study children at regular intervals after discharge from hospital to see if the improvement is sustained and whether there is a fall before further exacerbations. We also intend to look at changes over a longer period and examine possible relationships with clinical scores such as the Shwachman score.[11] Such a guide to 'everyday disability' may even be useful in contributing to the 'overall wellbeing' portion of the Shwachman score, which is extremely subjective.

We conclude that the two minute walking distance is a reproducible test which can be performed reliably by children as young as 5 years

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Acceptance of domiciliary theophylline monitoring using dried blood spots

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SUMMARY Filter paper cards incorporating dried blood spots for the measurement of theophylline concentrations were returned by 62 out of 100 asthmatic children sent kits with instructions for their collection. Analysis of the blood spots showed that 37 (61%) of the children who returned them had less than therapeutic blood theophylline concentrations, in 21 (34%) they were therapeutic, and in three (5%) they were potentially toxic. The results indicate that most asthmatic children would comply with requests for home monitoring of theophylline concentrations, and that only one third of children receiving theophylline achieved blood concentrations within the therapeutic range.

Theophylline is widely prescribed for the prophylaxis of bronchospasm in asthmatics but its use is attended by difficulties caused by its narrow therapeutic range, its potential toxicity, and its variable pharmacokinetics.[1 2] Prescriptions for theophylline are tailored mainly by the effectiveness of the relief of symptoms and the avoidance of side effects, but the monitoring of blood theophylline concentrations is a desirable part of treatment. Such monitoring can indicate compliance with and tolerance towards the prescribed dose, but requires patients to attend a hospital clinic or family practice for blood collection.

Dried blood spots have been used for the measurement of a number of substances including theophylline,[3–7] and their stability and convenience permit samples to be posted to the laboratory. Such methods are technically feasible, but their use depends upon the willingness of patients to provide samples. We have therefore examined the response of 100 asthmatic children and their families to a request for dried blood spots for theophylline assays. Analysis of the dried blood spots has provided information about blood theophylline concentrations in asthmatic children from samples collected at home.

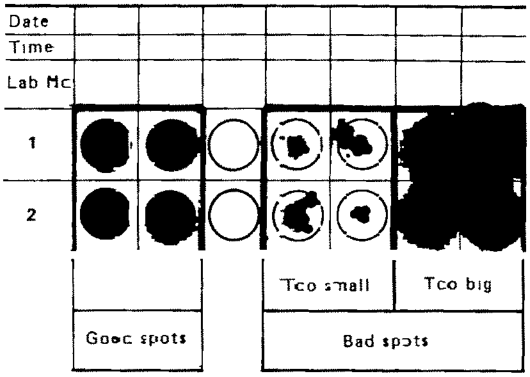
Patients and methods

Patients at the Sheffield Children's Hospital were identified as receiving theophylline from prescriptions dispensed by the hospital pharmacy and from requests for measurement of plasma theophylline concentrations received in the laboratory. One hundred outpatients were recruited into the trial from these sources over a period of six months. Written permission to study their patients was obtained from consultant paediatricians and approval for the trial was given by the hospital ethical committee. Patients' demographic details as well as their addresses, theophylline doses, and preparations taken, were extracted from the clinical records. All patients were asthmatics of varying degrees of severity and duration. Some were also receiving other medication for asthma.

Each patient entered into the trial was sent a kit addressed to 'the parent or guardian of . . . . . . ' that contained: a letter to the parent or guardian explaining the purpose of the trial; instructions for two fingerprick blood samples to be taken four hours after the morning dose of theophylline; a filter paper card to receive the blood spots with spaces for the patient's name, the date and time of sampling and of the last dose of theophylline to be entered; two sterile lancets; a photocopy of a filter paper card showing how correctly taken blood spots should look (figure); and an envelope with a first class stamp on it addressed to the laboratory.

If there was no response one month after sending the kit, a reminder letter was sent with panels for the parents or patients to tick to indicate why the sample had not been sent. The date of receipt of cards in the laboratory was noted and they were stored desiccated at −20°C.

Discs 6 mm in diameter were punched from dried blood spots taken from storage and analysed for theophylline by a method described elsewhere.[7]



Make sure your blood spots are good ones and fill the circles, or we will not be able to test them

Figure *Demonstration card sent out with collection kits showing how correctly taken blood spots should look.*

This consists of autoclaving the dried blood spots to fix protein, eluting theophylline with water and measuring it in the eluate by enzyme immunoassay (EMIT). Dried blood spots were considered suitable for analysis if the discs punched from them contained blood spread evenly over the whole of each side. Dried blood spots that did not fulfil these criteria were deemed unsatisfactory, and discs difficult to categorise were classed as doubtful. The batch to batch coefficients of variation of the assay for quality control samples run during the trial were 5·4% at 5·4 mg/l, and 6·3% at 18·6 mg/l. The derived therapeutic range of theophylline concentrations by this method is 7–14 mg/l. Plasma theophylline was measured by high performance liquid chromatography[8] with a therapeutic range of 10–20 mg/l.

Results

Of the 100 children recruited, 64 were boys and 36 girls with a median age at the time that the kits were distributed of 4 years 1 month (range 14 months to 15 years 9 months) (table). Seventy seven of the children were receiving sustained release theophylline preparations, 67 of the prescriptions being for Slo-phyllin (Lipha Pharmaceuticals Ltd, West Drayton), eight for Theo-Dur (Fisons plc, Loughborough), and two for Phyllocontin (Napp Laboratories Ltd, Cambridge). Nine children were receiving the non-sustained release preparation Nuelin (Riker Laboratories, Loughborough) and 14 children had stopped taking theophylline. The mean daily dose of theophylline was 300 mg with a range from 60 to 1350 mg for regimens that varied from one to four doses a day.

Cards incorporating dried blood spots were returned by 62 patients (62%). Forty eight (77%) of the cards returned had at least two satisfactory dried blood spots, and a further six (10%) contained at least one such spot. It became apparent that results from satisfactory and doubtful dried blood spots did not differ significantly and the latter were therefore included in the summarised results. Duplicate results were thus obtained from 56 cards (90%) and single results from five (8%) Only one card contained wholly unsuitable spots and these results were excluded from analysis. The mean time between kits being sent out and cards returned was 14 days, range 3 to 81. Reminders were sent to 33 patients who had not returned cards one month after the kits were dispatched, and six completed cards were returned after this.

Sixty (97%) of the cards returned had the date of collection of the dried blood spots recorded as requested. These gave a mean time of 2·1 days (range 0 to 9 days) between blood spot collection and receipt by the laboratory. The instructions sent out with the kits required that samples be taken four hours after the morning dose of theophylline and that these times should be recorded. Twenty five (40%) of the returned cards showed that this request had been complied with, but in addition three patients indicated that they had collected their

Table *Response rates and theophylline concentrations for dried blood spots requested from children at home*

Age group (years)	*No in trial*	*No (%) of cards returned*	*No of results within the therapeutic range of 7–14 mg/l[7] (% of 61 cards returned with satisfactory spots)*	*Dried blood spot theophylline concentrations (mean (SEM) mg/l)*
1·2–3	48	25 (52%)	10 (40%)	6 67 (0·85)
4–6	29	17 (59%)	6 (35%)	6 43 (0 86)
7–15	23	20 (87%)	5 (25%)	4 72 (0 99)
Total	100	62 (62%)	21 (34%)	5 96 (0·53)

samples five hours, one patient eight hours, and one patient nine hours after the last dose.

The mean dried blood spot theophylline concentration of the 61 patients whose cards could be analysed satisfactorily was 5·96 mg/l with a range of 0 to 15·7 mg/l. When concentrations were compared with the therapeutic range of 7 to 14 mg/l for this method,[7] 37 (61% of these children) had less than therapeutic concentrations, 21 (34%) had therapeutic concentrations, and three (5%) had concentrations above the therapeutic range. Of the 38 children who did not return spots, 12 were found subsequently to have discontinued theophylline and six parents informed us that they were unwilling or unable to collect the dried blood spots themselves. During the trial, and independently from it, 43 blood samples (32 outpatient, 11 inpatient) were sent to the laboratory from 38 of the chilren in the study for the measurement of plasma theophylline concentrations. Of these samples, 56% showed less than therapeutic concentrations, 42% showed therapeutic concentrations, and 2% showed concentrations above the therapeutic range for theophylline in plasma (10–20 mg/l).

Discussion

Various methods for the measurement of theophylline in dried blood spots have been reported[3–7] but there have been no studies to investigate the acceptance of dried blood spot samples by patients. In the present study 62 of 100 unselected paediatric patients complied with a request to send dried blood spots for theophylline assay. The true response rate, however, was 72% if the 14 patients who discontinued theophylline during the trial are excluded. This is a favourable response from families approached by letter alone, and may be compared with a response rate of 67% for a clinic based study of dried blood spot glucose estimations in diabetic children over 7 years of age.[9] Most of the samples received in the present study were suitable for duplicate analysis and only one returned card was completely unusable. This also compared favourably with the glucose study in which 17% of returned dried blood spots were unsuitable for analysis.

The proportion of boys to girls in the study and the age distribution were typical of asthmatic patients receiving theophylline in this hospital. The predominance of younger children (table) reflected the use of theophylline as prophylaxis in children too young to use inhalers. Compliance with the request to supply dried blood spots increased with age.

Instructions for collecting the dried blood spots gave no indication of urgency and if the cards come into general use, effort may be required to persuade patients to respond more promptly. On the other hand, the mean time between collection of the blood spots and return of the cards to the laboratory was acceptable at 2·1 days, as theophylline in dried blood spots is stable for at least one month.[6] Twenty five of the returned cards (40%) indicated that the specimen had been collected four hours after the last theophylline dose as requested, and these had a mean (SEM) concentration of 6·0 (0·81) mg/l. The mean concentration for dried blood spots from cards that did not carry this information was not significantly different (5·93 (0·71)) and this suggests that more patients complied with the required sampling time than those who recorded it on their cards. The proportions of all children who returned dried blood spots and who had theophylline concentrations that were less than therapeutic (61%), therapeutic (34%), or potentially toxic (5%) were similar to those who indicated that the samples were collected four hours after the last dose (64%, 32%, and 4% respectively), and both groups included fewer in the therapeutic range than the plasma theophylline concentrations requested for routine monitoring.

Studies in adults have shown that up to 70% of patients may have less than therapeutic concentrations of theophylline,[2 10] and in children 98% of those receiving a non-sustained release theophylline preparation were less than therapeutic.[11] The proportion of children with therapeutic concentrations decreased with age and did not include any over 11 years old. There was no correlation ($r=0·19$) between doses of theophylline prescribed and dried blood spot concentrations, with no improvement if only results from spots noted to have been collected four hours post dose are analysed. Six children had dried blood spot theophylline concentrations of less than 0·1 mg/l, suggesting that the theophylline prescribed was not being taken.

The results of this study are encouraging with regard to the willingness of paediatric patients and their parents to provide samples for dried blood spot analysis. Patients were only asked to take samples on one occasion and a more prolonged investigation would be required to see whether the response rate changed if regular sampling were requested. Supervision of the sampling arrangements from outpatient clinics might help to maintain compliance. The distribution of theophylline concentrations in the analysed dried blood spots supports previous reports that theophylline prescribing is conservative. It is recognised that the clinical response (such as an improvement in the forced expiratory volume in the first second) to prescribed theophylline is of prime importance, because symptoms may be relieved when circulating concentrations are below the therapeutic range.[12] Nevertheless the availability of a domiciliary monitoring service based on dried blood spot analysis would complement such assessment and give physicians additional confidence to prescribe an appropriate theophylline regimen.

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Low molecular weight IgM in juvenile chronic arthritis

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SUMMARY Low molecular weight IgM, the monomeric subunit of pentameric IgM, was clearly detected by immunoblotting and filtration chromatographic techniques in six patients with juvenile chronic arthritis and in trace quantities in a further eight of 24 patients studied. This low molecular weight IgM moiety contributed up to 33% of the total circulating IgM and was strongly associated with raised serum concentrations of IgM and the presence of antinuclear antibodies, extractable antinuclear antibodies, and rheumatoid factor. Immunoblot analysis of positive serum samples showed small quantities of other low molecular weight oligomers of IgM in addition to monomeric IgM. It is postulated that the presence of low molecular weight IgM in the serum of patients with juvenile chronic arthritis reflects a disorder of the intracellular assembly of IgM subunits during a stimulated IgM immune response. The pathogenetic role of low molecular weight IgM remains uncertain.

Low molecular weight IgM is the monomeric subunit of pentameric IgM, the latter being the normal circulating form of IgM. It is not found in serum from healthy adults but traces are seen in a few samples from neonates.[1 2] It is also described in certain autoimmune, infective, immunodeficient, and B cell lymphoproliferative disorders, and in these disorders low molecular weight IgM may constitute a considerable proportion of the total serum IgM.[1] The clinical significance of low molecular weight IgM is far from clear. Various acquired and autoantibody binding activities have been ascribed to this molecular moiety of IgM and its frequent occurrence in immune complex associated diseases suggests that it may have an important pathogenic role.[2] Furthermore its common association with chronic infective disorders such as chronic viral hepatitis[3] and syphilis[4] raises the possibility that it may be less efficient at clearing microorganisms from the host than the pentameric molecule; indeed, the agglutinating and precipitating activity of synthetically prepared low molecular weight IgM antibody is either weak or non-existent.[5]

Low molecular weight IgM has not been previously described in either healthy or diseased children. In this study we have observed its presence and that of other IgM oligomers in a number of patients with juvenile chronic arthritis, and have noted its association with certain autoantibodies and with raised serum IgM concentrations.

Patients and methods

Twenty four patients with juvenile chronic arthritis as defined by European League Against Rheumatism (EULAR) criteria were studied.[6] Of these, one girl had systemic onset disease, 19 children had pauciarticular onset (15 girls and four boys), and four had polyarticular onset (three girls and one boy). Seventeen of the patients had antinuclear antibodies (16 girls and one boy), and four had HLA B27 (three boys with pauciarticular onset, and one girl who also had antinuclear antibodies). Two girls with antinuclear antibodies and polyarticular onset also had weakly positive latex agglutination tests for rheumatoid factor, and one of these girls had an elder sister with rheumatoid arthritis. All patients had had active disease for at least one year before the study and most were taking non-steroidal anti-inflammatory drugs; several were also having agents to encourage remission (gold or penicillamine)

Control subjects comprised 15 healthy adults, five children with minor atopic disorders, and 21 immediate family members of the propositii (including 13 siblings). Blood was obtained by antecubital venepuncture in all instances and the serum samples were stored in small aliquots at −70°C.

Low molecular weight IgM was measured by two methods firstly, by gel filtration chromatography with IgM enzyme linked immunosorbent assay (ELISA). This was done as described by Koh *et al.*[7] Serum was chromatographed on a Sephacryl S300 90×1·5 column and the fractions analysed for IgM by competitive inhibition ELISA. A second IgM peak eluting just before the IgG marker position indicated the presence of low molecular weight IgM and its concentrations were quantified by planimetry.

The second method used was IgM immunoblotting. This was done as described by Harries *et al.*[8] Serum was subjected to sodium dodecyl polyacrylamide (3·6%) gel electrophoresis and the separated proteins transferred to nitrocellulose. IgM bands were identified with a μ chain specific antiserum (Dakopatts) and visualised with an avidin biotin, alkaline phosphatase, substrate system.

Serum IgM was measured by rate nephelometry (Beckmans ICS), which is not influenced by the size of the protein being quantified.[2] Antinuclear antibodies was measured by indirect immunofluorescence on HEp-2 cell line substrates using standard techniques All serum samples were initially screened at a dilution of 1:40 and a positive reaction recorded if nuclear fluorescence was detected at this dilution. Extractable antinuclear antibodies were measured by counterimmunoelectrophoresis in 1% agarose using rabbit thymus extract and K562 cell culture extract as the extractable antigens. Rheumatoid factor was assessed by latex agglutination (Behring). All these immunological techniques have been standardised and are in regular use in our department.

Results

Monomeric IgM was clearly evident in six patients and trace quantities were observed in a further eight patients with the immunoblot technique (table). Furthermore, small quantities (faint bands) of dimeric IgM and species migrating above and below this moiety were also evident in these six patients (fig 1) indicating the presence of other low molecular weight IgM oligomers. In each of these six patients the presence of low molecular weight IgM was verified by the filtration chromatography technique, which showed that it constituted between 10 and 33% of the total IgM as assessed by planimetry

Table *Association of low molecular weight IgM, autoantibodies and serum IgM in juvenile chronic arthritis*

	Low molecular weight IgM		
	Positive (n=6)	*Trace* (n=8)*	*Negative (n=10)*
Mean IgM concentration (g/l)	3·18	1·56	1·33
Antinuclear antibodies present	6	7	4
Extractable antinuclear antibodies present	4	1	2
Rheumatoid factor present	2	0	0

*Low molecular weight IgM band just visible on immunoblot

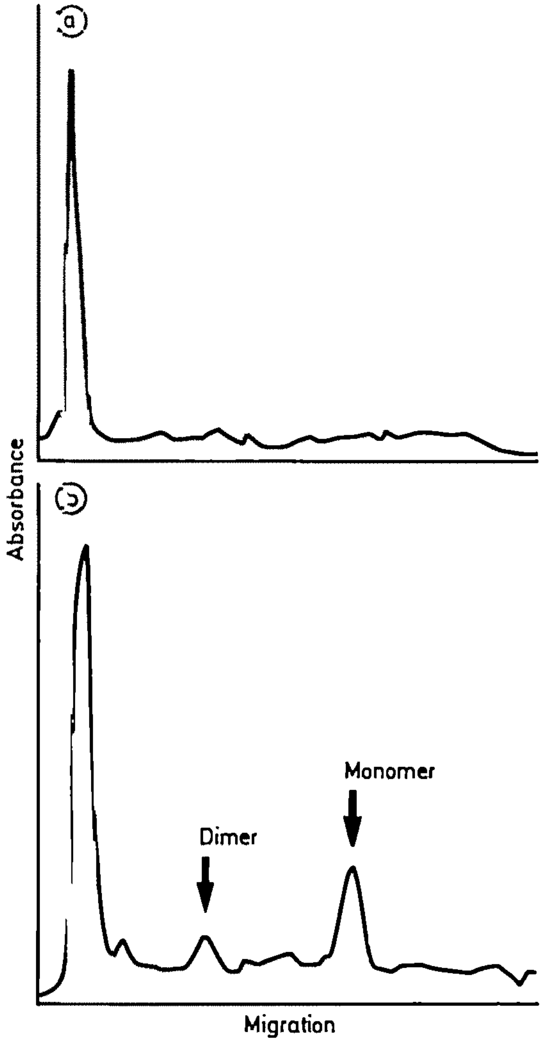

Fig 1 *Densitometric scan of immunoblot of serum from healthy control showing only the presence of pentameric IgM (panel a), and of serum from patient with chronic juvenile arthritis containing monomeric IgM and other low molecular weight IgM oligomers in addition to pentameric IgM (panel b).*

(fig 2). Of the six patients clearly positive for low molecular weight IgM, four had pauciarticular and two had polyarticular onset juvenile chronic arthritis, and all cases had detectable antinuclear antibodies with titres of 1:40 (four patients), 1:80, and >1:320. In addition, the mean serum IgM concentration for these patients was significantly higher than for the patients without low molecular weight IgM ($p<0 \cdot 01$, χ^2 test), four of these patients had undefined extractable antinuclear antibodies, and two had low titres of rheumatoid factor (latex agglutination 1:20) (table). In contrast, none of the 15 healthy adults or five atopic children had low molecular weight IgM as assessed by the filtration chromatography technique. Trace quantities of low molecular weight IgM were visible, however, using the immunoblot technique in two of the samples from the healthy adults and eight of the samples from the family members, and faint but clearly discernible low molecular weight IgM bands were observed in a further seven family members. Of these latter subjects, six were clinically asymptomatic, one had rheumatoid arthritis, and all but one had antinuclear antibodies or extractable antinuclear antibodies, or both, and had a mean serum IgM concentration of 1·64 g/l. None of the three boys with B27 associated juvenile chronic arthritis had either low molecular weight IgM or autoantibodies, but low molecular weight IgM was seen in one B27 positive girl who had pauciarticular onset juvenile chronic arthritis and antinuclear antibodies.

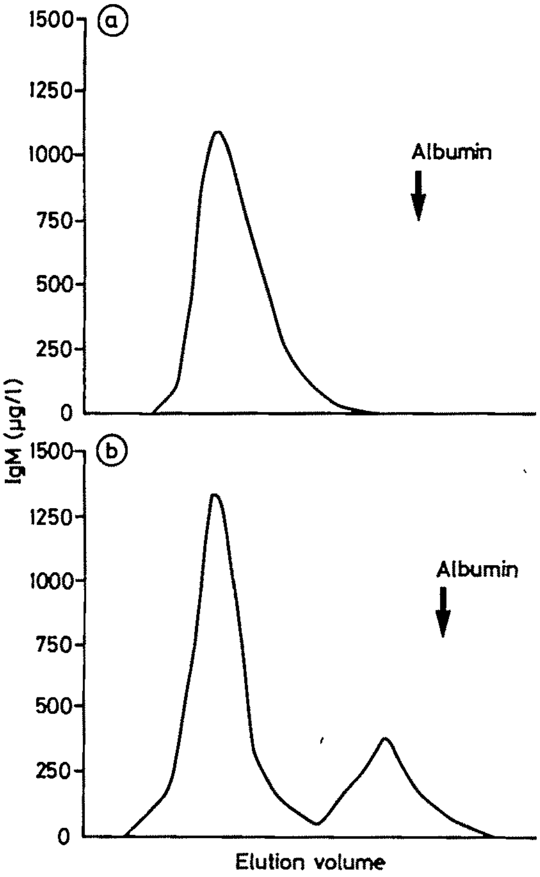

Fig 2 *Sephacryl S300 filtration chromatography IgM elution profiles. Eluting position of marker proteins are indicated. Panel a: serum from healthy control and panel b: serum from patient with chronic juvenile arthritis illustrating presence of low molecular weight IgM.*

Discussion

This study has clearly shown monomeric IgM and other low molecular weight IgM oligomers in six of 24 patients with juvenile chronic arthritis. Low molecular weight IgM seemed to occur most often in those patients with high serum concentrations of IgM and with the autoantibodies antinuclear antibodies, extractable antinuclear antibodies, and—to a lesser extent—rheumatoid factor. Small quantities of low molecular weight IgM and autoantibodies were also seen in other asymptomatic family members of these six patients, but were not seen in healthy adults or in five children with minor atopic disorders. No attempt was made in this study to correlate the quantity of low molecular weight IgM with clinical indices that reflected disease activity or severity because of the limited clinical data made available to the investigators.

The role of low molecular weight IgM in human disease is unknown.[2] It has been previously associated with a number of autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, and primary biliary cirrhosis, and is usually found in those patients who have more florid disease, often associated with high serum concentrations of IgM, autoantibodies, and immune complexes.[1] It has also been described in a number of chronic infective disorders including infective endocarditis,[7] chronic viral hepatitis,[3] and tertiary syphilis.[4] In the last two conditions, low molecular weight IgM occurs in a high proportion of affected subjects, in contrast to the acute initial infection where specific IgM is found only in the normal pentameric state. It is therefore possible that the presence of low molecular weight IgM leads to ineffective clearance of the micro-organism from the host, thereby facilitating chronic infection. Unfortunately in the current study we were unable to comment on the presence or absence of any possible infective illness either preceding the onset of the arthritic illness or immediately before the collection of blood samples for low molecular weight IgM analysis.

The finding of low molecular weight IgM in patients with juvenile chronic arthritis and in some of the family members in association with specific autoantibodies and high concentrations of serum IgM is of some interest. Traces of low molecular weight IgM are found only in serum samples from a few neonates, and never in serum from healthy adults.[9] Formal studies have not yet been performed in children but it seems highly unlikely that it will be found in healthy children. What then is the explanation for the occurrence of low molecular weight IgM in these children with juvenile chronic arthritis? A number of theories have been proposed to account for the presence of low molecular weight IgM in human disease.[7] It is not caused by a degradative process either in vivo or in vitro, and there is good evidence in certain diseases that it is actively secreted in the monomeric form in vitro.[10] The close association with high serum IgM concentrations (as are also found in a number of diseases in adults[1,2]) and the presence of other oligomers of IgM, suggest that its presence is a consequence of rapid rates of IgM synthesis and secretion with a resultant disturbance of assembly of the low molecular weight IgM subunit during polymerisation. Possible explanations for this disordered assembly could be alterations in the quantity or function of the J chain polypeptide that seems to play a vital part in polymerisation, structural alterations in the IgM monomeric subunit (for example, glycosylation defects), or alterations in the quantity or activity of the enzymes concerned in polymerisation (for example, sulphydryl oxidase[11]). In vitro studies using an IgM secreting human cell line are currently being performed in an attempt to examine some of these possibilities.

Does the presence of circulating low molecular weight IgM have any pathogenetic consequences in juvenile chronic arthritis? We cannot answer this question. In adults, however, there is good circumstantial evidence linking the presence of low molecular weight IgM to active or florid disease and—in the case of systemic lupus erythematosus—to increased mortality [12] Furthermore, several autoantibody activities, including antinuclear antibodies, have been ascribed to low molecular weight IgM. Hence we feel that a similar association may be found in juvenile chronic arthritis. If so, it will then be necessary to determine whether the presence of low molecular weight IgM is detrimental to the nature and course of patients with juvenile chronic arthritis, and see if there are any means of reversing the abnormal IgM humoral response so that it produces fully polymerised IgM (and thereby hopefully arrests the course of the disease)

In conclusion, we have observed the presence of low molecular weight IgM in patients with juvenile chronic arthritis for the first time and have suggested that its occurrence is associated with a disorder of assembly of the IgM subunits during IgM polymerisation.

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Chest pain of gastrointestinal origin

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SUMMARY Twenty seven children who had been diagnosed as having idiopathic chest pain were investigated to find out if the pain was of gastrointestinal origin. The symptoms had lasted from two weeks to eight months. In 21 of the 27 children (78%) the chest pain had a gastrointestinal cause: 16 had oesophagitis, four had gastritis, and one had diffuse oesophageal spasm. All patients responded to medical treatment of their gastrointestinal symptoms, resulting in disappearance of the chest pain.

Although chest pain is not usually associated with serious disease in children, if it occurs it is a cause of great anxiety for the patient and family. In one study 16% of children with chest pain made more than one visit to the accident and emergency department.[1]

Gastrointestinal disorders have not been described as being important causes of chest pain in children.[1-3] To further our understanding of the association between gastrointestinal dysfunction and chest pain in children, we carried out oesophageal manometry, oesophagogastroduodenoscopy, and Bernstein acid perfusion tests on 27 children with idiopathic chest pain, and extended ambulatory oesophageal pH monitoring on eight of the 27 patients.

Patients and methods

Fifty one patients between 8 and 20 years of age who complained of chest pain were investigated. All patients were initially examined by general paediatricians and the diagnoses were: idiopathic chest pain (n=27), musculoskeletal disorders (n=12), costochrondritis (n=9), and oesophagitis (n=3). Previously established criteria were used to make these diagnoses.[2]

The 27 children in whom a diagnosis of idiopathic chest pain had been made were further investigated by the division of paediatric gastroenterology at New York Medical College. The three patients with symptoms of oesophagitis were not included in the study. None of the patients had the characteristic symptoms of gastro-oesophageal reflux such as heartburn, regurgitation, pain on swallowing, dysphagia, haemorrhage, or 'water brash'. The chest pain was usually localised to the left praecordium, the central or retrosternal areas, or both, and episodes of pain lasted from less than a minute to several hours (table 1).

In order to determine the cause of the pain, each patient was investigated by oesophagogastroduodenoscopy, oesophageal manometry, and a Bernstein acid perfusion test. In addition, eight patients had extended ambulatory pH monitoring.

Oesophageal manometry was carried out with a triple lumen polyvinyl catheter assembly (individual outside diameter 1·2 mm) with three pressure sensing orifices separated by 5 mm. The catheter

Table 1 *Details of patients with chest pain of gastrointestinal origin*

	No (%) of patients
Age at onset (years):	
0–7	0 (0)
8–12	6 (28)
13–17	11 (52)
17–20	4 (19)
Duration of symptoms (months):	
<1	3 (14)
1–6	15 (72)
>6	3 (14)
Site of pain:	
Left praecordium	4 (19)
Central or retrosternal	4 (19)
Right praecordium	1 (4)
Combination (left praecordium and central or retrosternal	12 (57)
Duration of attacks (minutes)	
<1	4 (19)
1–5	8 (38)
6–60	6 (28)
>60	3 (14)

was perfused with sterile water at 0·5 ml/minute by a low compliance pneumatic hydraulic capillary infusion system with a pressure response of >106·8 kPa/second. Pressures were transmitted through the fluid filled catheters to transducers connected to a three channel polygraph recording system. The station pull through technique was used to determine lower oesophageal sphincter location and pressure. The normal range of lower oesophageal sphincter pressure in our laboratory is 2·0 to 4·0 kPa. To measure oesophageal peristalsis, 10 swallows of 5 ml water were given at 30 second intervals.

Abnormal oesophageal contractions were defined as: non-peristaltic contractions including simultaneous onset or the peaks of waves recorded at adjacent recording sites, and non-conducted swallows that caused no oesophageal pressure wave, or a wave too weak to be transmitted to the three recording sites; or repetitive contractions with the second and third peaks of more than 10% of the primary wave amplitude; or spontaneous contractions of more than 4·00 kPa that were not generated by swallows.[4] Wave amplitude expressed in kPa was measured from the mean intraoesophageal baseline pressure to the peak of the wave. Individual wave duration in seconds was measured from the onset of the principal upstroke to the end of the wave.

The Bernstein acid perfusion test was carried out by positioning the catheter in the upper third of the oesophagus. An infusion of 0·9% sodium chloride was given at a rate of 100 drops/minute for 10 minutes. This was followed by infusion of 0·1 mol/l hydrochloric acid for up to 10 minutes. The test was negative if the patient remained asymptomatic If severe discomfort was produced in the chest, the acid perfusion was stopped and saline reinstilled. Repeated elicitation of chest pain by acid perfusion followed by relief of symptoms on perfusion with saline indicated that the symptoms were due to the acid challenge.

Oesophageal pH monitoring was carried out by placing a pH monitoring probe in the mid-oesophagus after localisation of the lower oesophageal sphincter by oesophageal manometry.[5] Ambulatory pH monitoring was usually continued for 18 hours after placement of the probe.

Appreciable gastro-oesophageal reflux was diagnosed if there was a pH of less than 4 for 10% or more of the first two postprandial hours,[6] or if the mean duration of reflux during sleep was greater than four minutes more than two hours after feeding.[7]

Oesophagogastroduodenoscopy was carried out with an Olympus GIFXP10 gastroscope after sedation with meperidine and diazepam. Oesophagitis was diagnosed when the mucosa lost its normal vascular pattern and there was spontaneous friability, ulceration, or erythema. Gastritis was diagnosed when there was erythema, erosions, or bleeding. Oesophagitis[8 9] and gastritis[10] were graded histologically according to established criteria.

The protocol was approved by the office of research administration of New York Medical College Informed consent was obtained from the legal guardian of each patient.

Results

In 21 of the 27 patients a gastrointestinal cause was found for the chest pain. Sixteen of the 21 (76%) had oesophagitis and four (19%) had gastritis diagnosed both macroscopically and histologically. In one patient endoscopy was normal but there was diffuse oesophageal spasm on oesophageal manometry (table 2). Five patients with oesophagitis (31%) had abnormalities of oesophageal motility. Nine of the 16 with oesophagitis (56%) had lower oesophageal sphincter pressure that were significantly less (mean 9·44, SEM 0·75) than the mean of the group of patients with gastrointestinal chest pain (mean (SEM) 16·43 (1·54), $p<0·001$). The four patients with gastritis had a mean lower oesophageal sphincter pressure significantly higher (25·00 (1·41), $p<0·01$) than the group of patients with gastrointestinal chest pain. Eight patients with oesophagitis underwent prolonged oesophageal pH monitoring and all had appreciable gastro-oesophageal reflux. Nine patients with oesophagitis had positive Bernstein acid perfusion tests (table 3).

The patients with oesophagitis and gastritis had marked decreases in the severity of their chest pain within three weeks of starting activated dimethicone 0·5 mg/kg (maximum 30 ml/dose) one and three hours after meals, or ranitidine (150 mg twice daily) (table 4). Follow up endoscopies after two months of treatment showed that the oesophagitis and gastritis had resolved. The patient with diffuse oesophageal spasm had appreciably less chest pain after treatment with dicyclomine hydrochloride; permission to carry out repeat manometry, however, was refused (table 4).

Table 2 *Aetiology of chest pain of gastrointestinal origin*

	No (%) of patients
Oesophagitis	16 (76)
Gastritis	4 (19)
Diffuse oesophageal spasm	1 (5)

Table 3 *Results in 21 patients with chest pain of gastrointestinal origin*

Case No	*Appearance at endoscopy*	*Lower oesophageal sphincter pressure (kPa)*	*Oesophageal motility*	*Bernstein acid perfusion test*	*Prolonged oesophageal pH monitoring*
1	Gastritis	2·93	Normal	Negetive	No
2	Oesophagitis	1·33	Normal	Negative	No
3	Oesophagitis	1·20	Normal	Negative	No
4	Oesophagitis	2·40	Normal	Negative	No
5	Oesophagitis	3·47	Normal	Positive	Yes
6	Oesophagitis	0·933	Normal	Positive	Yes
7	Gastritis	3·33	Normal	Negative	No
8	Gastritis	3·73	Normal	Negative	No
9	Oesophagitis	1·60	Simultaneous contractions	Negative	No
10	Gastritis	3·33	Normal	Negative	No
11	Oesophagitis	2·93	Normal	Negative	Yes
12	Oesophagitis	2·67	Normal	Positive	Yes
13	Oesophagitis	1·07	Repetitive contractions	Positive	Yes
14	Normal	2·13	Diffuse oesophageal spasm	Negative	No
15	Oesophagitis	0·800	Simultaneous contractions	Positive	Yes
16	Oesophagitis	1·33	Normal	Positive	Yes
17	Oesophagitis	1·47	Normal	Negative	Yes
18	Oesophagitis	2·53	Normal	Positive	No
19	Oesophagitis	2·40	Simultaneous contractions	Positive	No
20	Oesophagitis	2·80	Simultaneous contractions	Positive	No
21	Oesophagitis	1·60	Normal	Negative	No

Table 4 *Treatment of chest pain of gastrointestinal origin*

	Activated dimethicone No (%)	*Ranitidine No (%)*	*Dicyclomine No (%)*
Oesophagitis	10 (62)	6 (38)	0
Gastritis	1 (25)	3 (75)	0
Diffuse oesophageal spasm	0	0	1 (100)

Discussion

Chest pain in children is usually described as idiopathic.[1-3] Gastrointestinal causes are rarely diagnosed, but systematic investigation of these children for gastrointestinal disease is not usually carried out. Studies in adults indicate that over half of the patients with angina like chest pain and normal coronary arteriograms are found to have oesophageal disorders.[11] The aetiology of such chest pain can be difficult to determine, because the heart and oesophagus have similar neural pain pathways. Both the cardiac plexus and the oesophageal plexus arise from the vagus nerves and sympathetic trunks.[11] We therefore performed gastrointestinal investigations in 27 children with 'idiopathic' chest pain. Twenty one of the children had gastrointestinal causes for their complaints. Abnormal oesophageal motility, oesophagitis, and gastritis were among the causes of non-specific chest pain.

Normal oesophageal motor activity consists of an orderly peristaltic contraction that passes through the oesophagus resulting in opening, and subsequent closing of the lower oesophageal sphincter. This progressive propulsive contraction of the oesophagus occurs in response to swallowing (primary peristalsis) or distension (secondary peristalsis).[12] Abnormalities of oesophageal peristalsis have been shown to produce symptoms of chest pain; one patient had difuse oesophageal spasm, which is particularly associated with chest pain.[13] It is characterised by simultaneous contractions after at least 10% of swallows of liquid during oesophageal motility testing, intermixed with normal peristaltic contractions.[13] Other abnormalities of peristaltic contractions are also associated with chest pain.[14]

Oesophagitis was the principal cause of chest pain in our patients. The most common clinical sign is heartburn, which is usually described as an uncomfortable burning sensation located below the sternum. Chest pain from oesophagitis, however, may be non-specific.[15] None of our patients with idiopathic chest pain had any of the characteristic symptoms of oesophagitis, and the diagnosis was made both endoscopically and on histological examination. Of the 16 patients with oesophagitis, five had associated abnormalities of oesophageal motility. Eight children with oesophagitis had prolonged oesophageal pH monitoring, which showed appreciable gastro-oesophageal reflux in each patient. All patients responded clinically to antacids or H_2 receptor antagonists. Follow up endoscopies carried out two months after the start of treatment were normal, indicating resolution of the oesophagitis.

Gastritis and peptic ulcer disease may also present as chest pain.[15] Four of the patients studied had both endoscopic and histological evidence of gastritis. *Campylobacter pylori* has recently been described as a cause of gastritis.[16] Future investigations of idiopathic chest pain in children should therefore include biopsy and culture for this bacterium. All our patients responded to treatment with an antacid or H_2 receptor antagonist, and so it is unlikely that *C pylori* was a cause. Repeat endoscopies after two months of treatment were also normal.

Our experience indicates that gastrointestinal causes of unexplained chest pain in children should be investigated. The symptoms of gastrointestinally induced chest pain are often non-specific, and can be determined with certainty only by oesophageal manometry and fibreoptic endoscopy. A patient with idiopathic chest pain may benefit from a therapeutic trial of an antacid before extensive gastrointestinal investigation is instigated.

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Hypertensive response to raised intracranial pressure in infancy

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SUMMARY Mean arterial pressure and intracranial pressure were measured serially in six infants with intracranial hypertension (intracranial pressure >20 mm Hg), and cerebral perfusion pressure was calculated from their difference. Overall, mean arterial pressure increased with rising intracranial pressure at a mean rate of 0·20 mm Hg/mm Hg. This caused a fall in cerebral perfusion pressure with increasing intracranial pressure at a mean rate of 0·80 mm Hg/mm Hg overall, although cerebral perfusion pressure was well maintained in one infant. Thus the rise in blood pressure was usually insufficient to compensate for the increase in intracranial pressure. In infants with acute encephalopathy vigorous blood pressure support is as important as lowering intracranial pressure.

Adequate perfusion of the brain is essential to its structural and functional integrity. Impairment of perfusion of the developing brain may have serious consequences resulting in death, or cerebral palsy with global or specific developmental retardation, blindness, spastic diplegia or quadriplegia, and fits.[1] Instability of perfusion has also been implicated as a cause of intraventricular haemorrhage.[2] The driving force of cerebral blood flow is the cerebral perfusion pressure, which is defined as the difference between mean arterial pressure and intracranial pressure.[3] This can be expressed as: cerebral blood flow=mean arterial pressure minus intracranial pressure/ cerebrovascular resistance.

Autoregulation may be defined as the process by which cerebral blood flow is maintained in the face of any alteration of cerebral perfusion pressure.[4] In its absence, cerebral blood flow is proportional to cerebral perfusion pressure, and is said to be pressure passive. It is thought to occur mainly through variations in cerebral arteriolar tone[4]: vasodilatation reduces cerebrovascular resistance, which tends to increase cerebral blood flow.

In the case of raised intracranial pressure, vasodilatation may act to maintain cerebral blood flow,[5 6] but an alternative means of compensation is available. Cushing[7] first described the rise in blood pressure that occurs under these circumstances. It may be achieved by increasing cardiac output, but sympathetically mediated peripheral vasoconstriction is thought to be a more important mechanism.[8 9] Cushing's phenomenon has been described many times in animals[6 8–11] and older humans.[12] It comprises a progressive increase in blood pressure once the intracranial pressure has attained a variable level that is approaching the resting arterial diastolic pressure.[6–9 11] At very high or sustained levels of intracranial pressure the response is exhausted, and blood pressure falls.

When both compensatory mechanisms (cerebral arteriolar dilatation and Cushing's response) operate during rises in intracranial pressure, a three step pattern of blood pressure change has been observed in experimental animals and humans.[5 6 10–12] Firstly, as the intracranial pressure rises above the normal range cerebral arteriolar vasodilatation occurs, with no change in mean arterial pressure and a steady fall in cerebral perfusion pressure; secondly, when the Cushing range is attained, the mean arterial pressure rises steadily and the cerebral perfusion pressure is maintained; and thirdly when the latter is eventually exhausted, mean arterial pressure and cerebral perfusion pressure both fall (the latter often into the negative range).

It is not known whether the Cushing response occurs in young subjects. In two studies of newborn dogs there was no increase in arterial pressure with rising intracranial pressure,[13 14] and a Cushing response was seen only in two of a series of 14 asphyxiated babies.[15] A classical Cushing response, however, has been seen in newborn rabbits.[11] The aim of the current study was to investigate the association of blood pressure and intracranial pressure in a group of infants at risk of developing intracranial hypertension in order to determine to what extent a rise in intracranial pressure was accompanied by an increase in blood pressure.

Methods

Twenty infants in the Hammersmith Hospital neonatal unit at risk of developing intracranial hypertension underwent simultaneous serial intracranial and blood pressure measurements over a two and a half year period. Only those six whose peak intracranial pressure reached >20 mm Hg are considered in further detail because previous work has suggested that the Cushing phenomenon only occurs when the intracranial pressure is considerably raised. The clinical characteristics of this subgroup are shown in the table. Compared with the group as a whole, they were significantly older (median 15·5 weeks compared with 3 days postnatal age) but there were no differences in birth weight or gestational age. This probably reflects the decreasing skull compliance of the older subject as the cranial sutures fuse, permitting a higher intracranial pressure to be achieved.

Blood pressure was measured from an indwelling arterial catheter when available, yielding 236 measurements. Pressure was measured by a Gaeltec transducer (Gaeltec Ltd) coupled to a Tektronix monitor (Tektronix Inc) or by a Gould transducer (Gould Statham Instruments Inc) coupled to a Medifax monitor (Cardiac Recorders Ltd) attached to the catheter. The values were accepted only when the pressure wave showed a dicrotic notch and the difference between the systolic and diastolic pressures was >10 mm Hg; otherwise damping caused by air bubbles or blood clot was suspected and corrected. In the absence of an arterial catheter in 110 observations, an appropriately sized Dinamap cuff (Critikon Ltd) was applied to a convenient limb and blood pressure measured oscillometrically. This technique has been validated against invasive blood pressure measurement.[16]

Intracranial pressure was measured by connecting a Gaeltec transducer coupled to a Tektronix monitor to a cerebrospinal fluid cannula inserted for clinical indications. This was a subarachnoid catheter (Levene and Evans[17]) for 340 data points in five babies, and a ventricular cannula for six observations in one. Care was taken to exclude bubbles from the measuring circuit, to minimise leakage of cerebrospinal fluid, and to establish craniospinal communication where relevant.[18] The cerebrospinal fluid wave was displayed and the pressure recorded from the digital readout using the mean if the pulse pressure was perceptible.

In babies with indwelling intracranial pressure catheters the two pressures were taken simultaneously every half to one hour. Otherwise the blood pressure was measured immediately before positioning the child for ventricular puncture, or as soon after its conclusion as required for the baby to be settled. Babies were nursed horizontally. The right atrium was used as the pressure reference point. The transducers were calibrated immediately before connection and after disconnection and at six to 12 hourly intervals in between. Cerebral perfusion pressure was calculated as the difference between mean arterial pressure and intracranial pressure.

Table *Clinical details of six patients whose peak intracranial pressure reached >20 mm Hg*

Case No	*Diagnosis*	*Gestation (weeks)*	*Age (weeks)*	*Range of intracranial pressure measurements (mm Hg)*	*No of invasive mean arterial pressure measurements*	*No of oscillometric mean arterial pressure measurements*	*Gradient of regression lines*	
							Mean arterial pressure	*Cerebral perfusion pressure*
6	Surgical asphyxia	35	26	6–50	185	0	0·28	−0·73
7	Surgical asphyxia	32	5	5–21	0	23	−0·36	−1 36
8	Surgical asphyxia	34	30	10–36	0	44	1·83	0·83
9	Asphyxia caused by respiratory distress syndrome	33	0–1	7–35	48	0	−0·24	−1·24
13	Intracranial haemorrhage	40	0	12–36	3	37	−0 08	−1 08
17	Post haemorrhagic ventricular dilatation	28	43	6–51	0	6	−0 21	−1·21
Median (range)		33 5 (28–40)	15 5 (0–43)	18 (5–51)	—	—	—	—
Mean		—	—	—	—	—	0·20	−0 80

A total of 346 observations was made, between six and 185 (median 44) for each child.

Results

The association of the dependent variables with intracranial pressure were considered separately for each subject. The only obvious correlation obtained was linear over the entire data range, rather than the three step curve described above, and fig 1 shows the best fit lines for one of the babies (case 6) recovering from operative hypoxia.

Fig 2 shows the association between mean arterial pressure and intracranial pressure in the babies in the high intracranial pressure subgroup. The gradient of the lines was close to 0 in most. The slopes ranged between −0·36 and 1·83 (mean 0·20) mm Hg for each mm Hg increase in intracranial pressure.

One baby (case 8) showed an exceptional rise in blood pressure with rising intracranial pressure, sufficient to maintain an increase in cerebral perfusion pressure. He was distinguished from the rest of the subgroup by being one of the oldest, and by having suffered a comparatively short and minor asphyxial insult.

Fig 3 shows that cerebral perfusion pressure fell with rising intracranial pressure in all the other five babies. The mean rate of fall in these was 1·12 (range 0·73 to 1·36) mm Hg for each mm Hg rise in intracranial pressure. Including all the babies, the mean rate was 0·80 mm Hg/mm Hg.

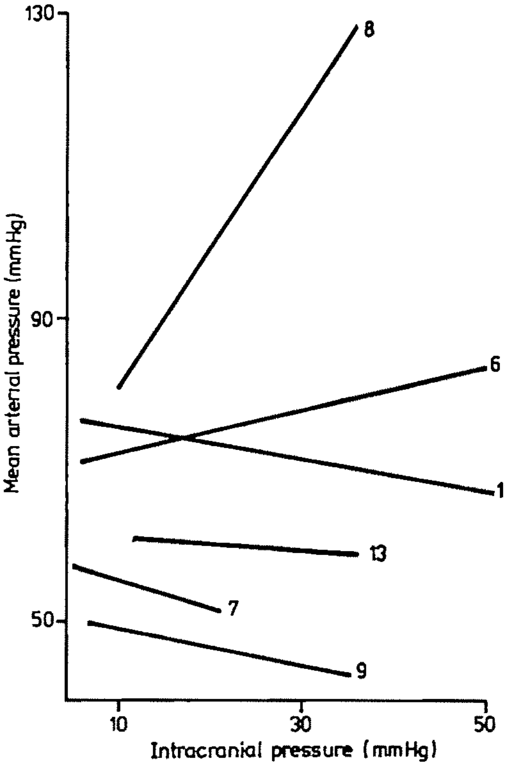

Fig 2 *Regression lines of mean arterial pressure on intracranial pressure for the six patients studied.*

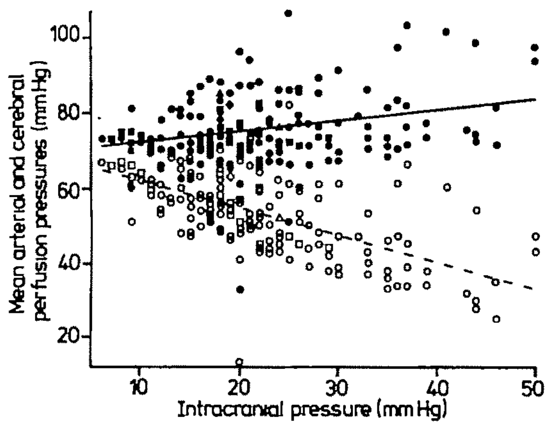

Fig 1 *Correlation of mean arterial pressure (closed symbols and solid line) and cerebral perfusion pressure (open symbols and broken line) with intracranial pressure in case 6. Individual data points are represented by circles, two coincident points by squares, three by triangles and four by diamonds. The data are correlated thus. mean arterial pressure=69 412+0·277 intracranial pressure, r=0·289, p<0·001, cerebral perfusion pressure=69·412–0·723 intracranial pressure, r=−0·619, p<0·001; df=183 and SE of estimate=8·328 for both.*

Discussion

In the first study of the influence of intracranial pressure on blood pressure in the human infant we have shown that mean arterial pressure and cerebral perfusion pressure have a linear correlation with intracranial pressure. The exact correlation of mean arterial pressure to intracranial pressure, however, was inconsistent and usually rose inadequately to maintain cerebral perfusion pressure.

Does this mean that the Cushing response does not occur in human infants? On one hand, intracranial pressure may not have risen high enough to elicit a Cushing response. In the current series, the peak intracranial pressure was 20–45 mm Hg below the resting mean arterial pressure (calculated from the regression line projected back to the region where the intracranial pressure was normal). In the neonatal animal and older human, however, mean arterial pressure begins to rise only when intracra-

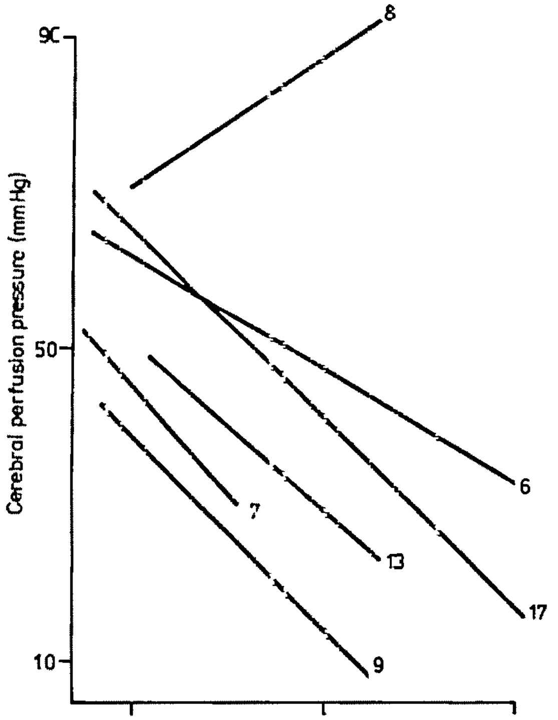

Fig 3 *Regression lines of cerebral perfusion pressure on intracranial pressure for the six patients studied*

nial pressure is within 10–15 mm Hg of it. If the human infant behaves similarly, a Cushing response would be unlikely in the intracranial pressure range achieved. On the other hand, one baby seemed to evince a Cushing response despite the intracranial pressure levels being well below resting blood pressure (35 mm Hg at peak intracranial pressure).

Failure of the Cushing response could occur by several mechanisms, individually or in combination. For a completed response the following steps are necessary: detection of intracranial hypertension; afferent conduction; vasomotor centre activation; efferent (sympathetic) conduction; increase in cardiac output (by increased stroke volume or increased heart rate, or both) or increase in peripheral vascular resistance, or both. An increase in cardiac output is thought to be of minor importance in the production of the Cushing response. In the current series the finding that cardiac output often required support by colloid infusion and inotropic agents is further evidence that this mechanism is of little practical value in the infant. It is unlikely that peripheral vasomotor tone is impaired, because generalised vasoconstriction is a cardinal feature of the asphyxiated subject, one of the groups best represented in this study. It could be argued that our subjects were already maximally vasoconstricted, but they did not seem to be. Alternatively the requirement of many babies for colloid and inotropic support might have indicated a reduced cardiovascular reserve, but they subsequently seemed normovolaemic and the inotropic treatment was brief and low doses were given. This inculpates the afferent and efferent pathways and the vasomotor centre. Any of these may be impaired by the neurological insult, by the intracranial hypertension itself, or merely by their immaturity.[11]

The magnitude of the fall in cerebral perfusion pressure as the intracranial pressure increases is only important in so far as it might determine the level of intracranial pressure at which cerebral blood flow falls below a critical level. Goitein *et al*[19] suggested that cerebral perfusion pressure should be maintained above 30 mm Hg in the first six months and 40 mm Hg thereafter, and Raju *et al*[15] observed in 14 asphyxiated newborns that the minimum safe level of cerebral perfusion pressure was 25 mm Hg. In our series, observed or extrapolated values of cerebral perfusion pressure fell below these levels at intracranial pressure between 11·9 and 60·2 mm Hg. Thus an intracranial pressure value at only twice the upper limit of normal of 6 mm Hg[18] could reduce cerebral perfusion pressure by a critical amount. Such rises may occur quite readily during episodes of intracranial hypertension in the newborn.

An interesting finding in our series was that in the two infants in whom a dangerously low cerebral perfusion pressure occurred (cases 9 and 17, whose lowest cerebral perfusion pressure values were 5 and 15 mm Hg), the outcome was poor: they both had severe development delay with spastic quadriplegia, blindness, and fits associated with widespread cortical atrophy.

Management of the acute encephalopathies of infancy should take the anomalous behaviour of the Cushing response into account. The behaviour of the blood pressure and the intracranial pressure should be considered together in case the Cushing response is inadequate. The combination of rising intracranial pressure and falling cerebral perfusion pressure requires the vigorous support of blood pressure and reduction of intracranial pressure.

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Choreic syndrome after cardiac surgery

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SUMMARY Five children had an acute choreic syndrome that started three to seven days after hypothermic cardiopulmonary bypass surgery. Improvement after an interval was seen in all, with complete resolution in two. In addition to the chorea, all children suffered complete supranuclear ophthalmoplegia, which has also shown subsequent improvement. Bulbar damage caused considerable speech problems There was no cognitive impairment. Several drugs were tried without effect. Investigations of the cause, including histological examination, have been unrevealing.

The onset of acute chorea is both dramatic and profoundly disturbing, it can arise in various settings. The clinical signs of carbon monoxide poisoning, Wilson's disease, Leigh's disease, local tumours, inflammatory processes, demyelinating or ischaemic lesions are not difficult to understand, because they originate in the basal ganglia. In classic post streptococcal Sydenham's chorea the explanation may lie in the fact that the cytoplasm of the cell bodies in the caudate and subthalamic nuclei seem to be antigenically similar to the streptococcus.[1] Chorea precipitated by pregnancy or the contraceptive pill may be a result of the effect of oestrogens on dopaminergic activity of basal ganglia.

Chorea after hypothermic cardiac bypass has occasionally been described,[2–7] but only in childhood We report five additional children with a strikingly sterotyped presentation and course, having in common intriguing additional clinical features We hope that by drawing attention to this distressing condition we will encourage others to report similar cases and thereby stimulate attempts to identify its cause.

Patients and methods

Five cases presented at the Brompton Hospital during an 18 month period from July 1985. Cardiological data were extracted from the hospital records by careful scrutiny of the anaesthetic and operative records. Cases 1–4 were under the neurological care of ROR, and details of the fifth child were taken from the case notes of the Hospital for Sick Children, Great Ormond Street.

Results

Ages at the time of cardiopulmonary bypass ranged from 4 months to 6 years. Except for the one child with Down's syndrome (case 5) all children had developed normally before operation. Cardiac defects in the individual cases are shown in table 1 together with the total time spent on cardiopulmonary bypass, the time of circulatory arrest, and the minimum core temperature. The operation was without untoward incident in all cases, as was the immediate postoperative recovery. The onset of chorea occurred after a latent period of clear normality varying between three to seven days after operation. One child (case 1) was sufficiently recovered to be discharged home before the onset of the chorea, and another (case 4) was noted to be enunciating clearly around the endotracheal tube before extubation at five days. The onset of chorea was comparatively abrupt, but its frequency and amplitude increased over thé first three to five days. It then remained continuous while the child was awake, being sufficiently disturbing to preclude sleep, during which the movements disappeared Trials of several drugs including haloperidol, tetrabenazine, sodium valproate, benzhexol, and carbamazepine were ineffective unless given in sufficiently large doses to induce sleep. Improvement in the chorea began at periods varying from two days to eight weeks (table 2). The chorea had resolved completely after two weeks and six months in cases 2 and 4, respectively, but was residually present but continuing to improve in the other two survivors (cases 1 and 3) by nine and 19 months,

Table 1 *Details of five patients studied*

Case No	*Sex*	*Age at cardiopulmonary bypass*	*Cardiac lesion*	*Bypass time (minutes)*	*Circulatory arrest time (minutes)*	*Minimum core temperature (°C)*
1	F	1 year 5 months	Transposition great arteries, ventriculoseptal defect	208	2 and 5	15
2	F	4 months	Ventriculoseptal defect	29	29	15
3	F	3 years	Ventriculoseptal defect, atrioseptal defect, anomolous pulmonary venous drainage	132	26	15
4	M	6 years	Ventriculoseptal defect, pulmonary atresia	130	16	15
5	F	8 months	Fallot's tetralogy	89	45	9

Table 2 *Details of choreic syndrome after cardiac surgery*

Case No	*Onset of chorea and supranuclear ophthalmoplegia after bypass*	*Onset of recovery of chorea*	*Resolution of chorea*	*Duration of complete supranuclear ophthalmoplegia*	*Complete resolution of supranuclear ophthalmoplegia*	*Duration of follow up*
1	7 days	3 weeks	Residually present at 19 months	4 months	Not by 19 months	19 months
2	3 days	2 days	2 weeks	2 days	2–4 weeks	9 months
3	3 days	2 weeks	Residually present at 9 months	6 weeks	Not by 9 months	9 months
4	6 days	8 weeks	6 months	5 months	7 months	9 months
5	3 days	1–3 months	Small amplitude movement by 4 months	3 months	Not by 4 months	Died 5 months after surgery

respectively. Both regained the ability to walk and feed themselves, albeit unsteadily. The child with Down's syndrome died unexpectedly at home five months after operation, at a time when the chorea was still present although diminishing.

The onset of chorea was accompanied by a generalised loss of tone. With the exception again of the youngest child this persisted (although diminishing) in the other three survivors Deep tendon reflexes in all were initially difficult to obtain. In the youngest child there was a visible loss of anal tone, which recovered after 72 hours The oldest child became incontinent for three months, and case 3 still had urgency of micturition nine months later.

At the same time as the onset of chorea all children suffered a complete supranuclear ophthalmoplegia Doll's eye reflexes remained full but voluntary directed gaze was lost. With the exception of the youngest child (in whom return of voluntary eye movements was the first sign of recovery) improvement of voluntary eye movements began some time after the onset of recovery of chorea (table 2). During the recovery period there was a decreasing latent period before the onset of voluntary eye movement, which was then interrupted by coarse saccades. Smooth tracking was achieved in only two patients (cases 2 and 4). Vertical eye movements seemed to recover at the same rate as horizontal eye movements.

All children experienced difficulty with feeding; the onset of this was abrupt in all but the eldest, in whom it evolved over a three week period. In this child the tongue became contracted and comparatively immobile. In the remainder our impression was that the bulbar chorea precluded effective coordination of sucking and swallowing Improvement in feeding dated from the improvement in chorea elsewhere.

Understanding of speech and situation remained intact throughout in all. There was no evidence of mental impairment in any case. Production of speech was, however, severely impaired in two (cases 3 and 4) despite complete resolution of the chorea in case 4, and remained mildly impaired in case 1, 19 months after operation. The youngest child who has completely recovered is still only 13 months old.

Laboratory tests at the time of the acute onset of illness in all included routine haematological investigations, estimation of the concentrations of electrolytes (including calcium and magnesium) and blood glucose, liver function tests, and clotting studies. Results were normal in all cases. Similarly, examination of the cerebrospinal fluid (in four) and computed tomography of the brain (in three) were also normal. Additional investigations including estimation of neurotransmitter metabolites and concentrations of folic acid in the cerebrospinal fluid, ammonia in the blood, erythrocyte sedimentation rate, and aspartate transaminase activity were all normal as were electroencephalography and measurement of auditory and visually evoked potentials.

Neuropathological examination of the brain of the child with Down's syndrome showed no features in addition to those of Down's syndrome. In particular there was no abnormality of the basal ganglia.

Discussion

Although neurological complications after cardiac surgery are often discussed together they are clearly a disparate collection of diseases with different causes and varying outcomes. For many, the cause is readily apparent being either embolic, hypoxic or ischaemic, or haemorrhagic, and the lesion is usually visible on computed tomography. The clinical picture is defined by the vascular territory or parts of the brain involved. Thus with the exception of severe and diffuse hypoxic or ischaemic damage, the distribution of neurological signs varies from case to case.

Chorea following cardiopulmonary bypass does not come into any of these classifications. Although transient, comparatively mild unwanted movements are not uncommon after cardiac surgery, the full blown syndrome as described here is rarely reported. Because the clinical picture is so striking it cannot go unrecognised and is therefore unlikely to be underreported. The first description we can find was by Bjork and Hultquist in 1960.[2] They reported the neurological effects of deep hypothermia in eight children and three adults. Only two children in their series seemed to have survived operation.

Three of their children who died bore some resemblance to our cases with extrapyramidal signs appearing after the first few days. Clinical details, however, are sparse. Since then a further 12 cases have been reported, the most detailed clinical description being that of Brunberg *et al* in 1974, who recognised four such children in a series of 22 infants aged less than 24 months.

The clinical picture of these 17 and our five cases is rather stereotyped. No case to our knowledge has been reported outside early childhood, and the onset is from two to seven days after operation. Though it is possible that in some of these cases the onset may have been suppressed by necessarily heavy sedation in the immediate postoperative period, in most there was a clear period of normality beforehand. The severity of the chorea progressed over one to three weeks with the exception of our case 2 (the youngest child so far reported) who began to recover after 24 hours, and affected the face, bulbar muscles, and all four limbs. Where clinical details are sufficient to allow a conclusion, the tone seemed to be poor both in trunk and limbs, with reflexes either normal or suppressed. Drawing only from the previous clinical series some recovery seems to have taken place in all, with three previous cases recovering completely. Follow up periods vary, however, and insufficient information is currently available on which to base a firm prognosis.

One of the most unusual features of our cases was the oculomotor apraxia. Directed gaze in these children was only possible initially by movement of the whole head. Subsequently there was a noticeable lag before the onset of conjugate deviation with scanning, interrupted by coarse saccades; although consistent in our cases, this has not previously been noted. Because, however, note was made of 'random' or 'irregular shifting' eye movements it may have been present in other series but misinterpreted

An apractic element may limit other functions accounting particularly for the speech delay. This might be difficult to distinguish in the younger children in the presence of unwanted movements. Our case 4 who was 6 years old at the time of surgery was able to mimic a wide repertoire of mouth and tongue movements at a time when he was virtually anarthric. During this period he was able to copy a written sentence accurately, but unable to organise the same sequence of words on a blank page. Dressing apraxia was not a feature nor did use of eating utensils or scissors provide any difficulty in addition to that expected from his chorea

It is possible to think of a wide variety of possible pathogenetic mechanisms, including undetected hypoxia, or reduced perfusion from undetected hypocarbia or hyperviscosity. Immunological explanations entailing release of cardiac antigen and breakdown of blood brain barrier are difficult to sustain in the face of the short latent period before the onset of the movement disorder. Idiosyncratic reactions to drugs (including anaesthetic agents) are similarly untenable. Although a variety of drugs and pressor agents were used no one agent was common to all. All children had undergone previous procedures necessitating the use of anaesthetics, and one child had had a previous hypothermic bypass procedure (case 4).

Because computed tomography in the three of our cases in which it was carried out and in both Diebler and Dulac's two cases was normal,[7] structural damage if it occurs must be extremely focal and discrete; we failed, however, to identify any histological changes in our one case that came to necropsy.

The latent period is equally difficult to account for. The timing before onset is similar to that of delayed onset hypoxic encephalopathy, and the pathogenesis is similarly obscure. It is conceivable that sufficient cellular damage occurs to interrupt neurotransmitter synthesis or reuptake, the onset of symptoms coinciding with depletion of intracellular stores. Chorea has been attributed to excessive dopaminergic activity. This excess activity may, however, only be so in comparison with that of other neurotransmitters such as acetyl choline. The suggestion of, for example, impermanent depletion of basal ganglia and frontoparietal acetyl choline is one possible explanation consistent with normal concentrations of 5-hydroxy indole acetic acid, 5-methoxy 4-hydroxy phenyl glycol, and homovanillic acid in cerebrospinal fluid, the ineffectiveness of therapeutic trials to date, and the oculomotor apraxia.

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Non-invasive method for early diagnosis of herpes simplex encephalitis

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SUMMARY For the early diagnosis of herpes simplex encephalitis IgG and IgM antibodies to herpes simplex virus in cerebrospinal fluid were measured by an enzyme linked immunosorbent assay (ELISA) and a local production index was calculated. Using these three criteria, 31 cases of various neurological illnesses were analysed. All eight cases of herpes simplex encephalitis were diagnosed correctly in the acute phase, and there were no false positive results.

The prognosis of herpes simplex encephalitis has been improved since the introduction of antiviral agents such as acyclovir and vidarabine.[1] Early diagnosis is therefore important. Although detection of herpes simplex virus antigen in a brain biopsy specimen is one of the most reliable methods of early diagnosis this is not always possible because of the risk of side effects. We have previously investigated the intrathecal synthesis of antibodies in mumps meningitis, and have shown that the ratio of antibodies in cerebrospinal fluid to that in serum (C:S ratio) was moderately increased by the intrathecal synthesis of antimumps antibodies.[2] Levine *et al*[3] reported that the C:S ratio of antibodies against herpes simplex virus was more than 1:20 in herpes simplex encephalitis, and that the amount of local production of antibodies could indicate the diagnosis early. In some neurological disorders, however, the serum can escape into cerebrospinal fluid across the damaged blood brain barrier, and this could lead to misdiagnosis of herpes simplex encephalitis. As well as detecting IgG and IgM antibodies to herpes simplex virus in cerebrospinal fluid with an enzyme linked immunosorbent assay (ELISA), we have also calculated a local production index that enables us to eliminate the influence of antibodies in the serum, thereby giving an accurate diagnostic test for herpes simplex encephalitis.

Patients and methods

Paired samples of serum and cerebrospinal fluid were obtained from 31 patients (0 to 16 years of age) with various neurological illnesses within 10 days of the onset of neurological signs. The patients were divided into two groups, eight who had herpes simplex encephalitis and 23 who did not. The latter group included four with measles encephalitis, three with enterovirus encephalitis, two with varicella encephalitis, one with mumps encephalitis, one with subacute sclerosing panencephalitis, and nine with encephalitis of unknown cause; in addition there was one case each of Guillain-Barré syndrome, brain tumour, and brain abscess. The diagnosis of herpes simplex encephalitis had been made on clinical findings, the results of electroencephalography and computed tomography, and the pronounced serological response in serum samples and cerebrospinal fluid.

Antibody activities against herpes simplex virus were examined by ELISA using a modification of the method described by Sakata *et al.*[4] Herpes simplex virus type 1 (HF strain) were grown in vero cells and purified by continuous sucrose gradient centrifugation; a 96 well flat bottomed microplate (Immunoplate II, Nunc, Denmark) was coated with the purified virus at a protein concentration of 2·5 µg/ml. After diluted serum samples (1/100) and samples of cerebrospinal fluid (1/5) were put into the wells, peroxidase conjugated antihuman IgG or IgM goat serum (Tago Inc, California, USA) were added as secondary antibodies. For the standardisation of ELISA titres, twofold serial dilution of standard pooled serum samples were measured in each assay. The antibody titres of the samples were calculated from the dilution of standard serum which indicated the same absorbance as those of the samples. To evaluate the influence of the antibody that escaped across the damaged blood brain barrier on the activity of cerebrospinal fluid antibodies we measured the antibody titres against mumps virus as a control, and the C:S ratios were compared with those of the antibody against herpes simplex virus. The formula used to calculate the local production index was: amount of IgG antibody against herpes simplex virus in the cerebrospinal fluid minus the amount of IgG antibody against herpes simplex virus in the serum multiplied by the C:S ratio of mumps antibody. This expressed the actual titre of antibody that was synthesised intrathecally. Statistical analysis was by Student's *t* test.

Results

IgM and IgG antibodies to herpes simplex virus in cerebrospinal fluid were measured, and the local production indexes were determined. There were significantly higher titres in each category in patients with herpes simplex encephalitis compared with those with other neurological disorders ($p<0{\cdot}01$, $p<0{\cdot}01$, and $p<0{\cdot}05$, respectively) (figure). From these results the following criteria were defined for the early diagnosis of herpes simplex encephalitis· (1) a high titre of IgG antibody to herpes simplex virus in the cerebrospinal fluid (mean plus standard deviation above the value for patients who did not have herpes simplex encephalitis); (2) a positive titre of IgM antibody to herpes simplex virus in the cerebrospinal fluid (mean plus two standard deviations above the value for patients who did not have herpes simplex encephalitis; and (3) a high local production index (mean plus standard deviation above the value for patients who did not have herpes simplex encephalitis). When at least two of the three criteria were found in the acute phase, the patient was provisionally diagnosed as having herpes simplex encephalitis.

Using these criteria, 31 cases of neurological illnesses were examined retrospectively (table). All

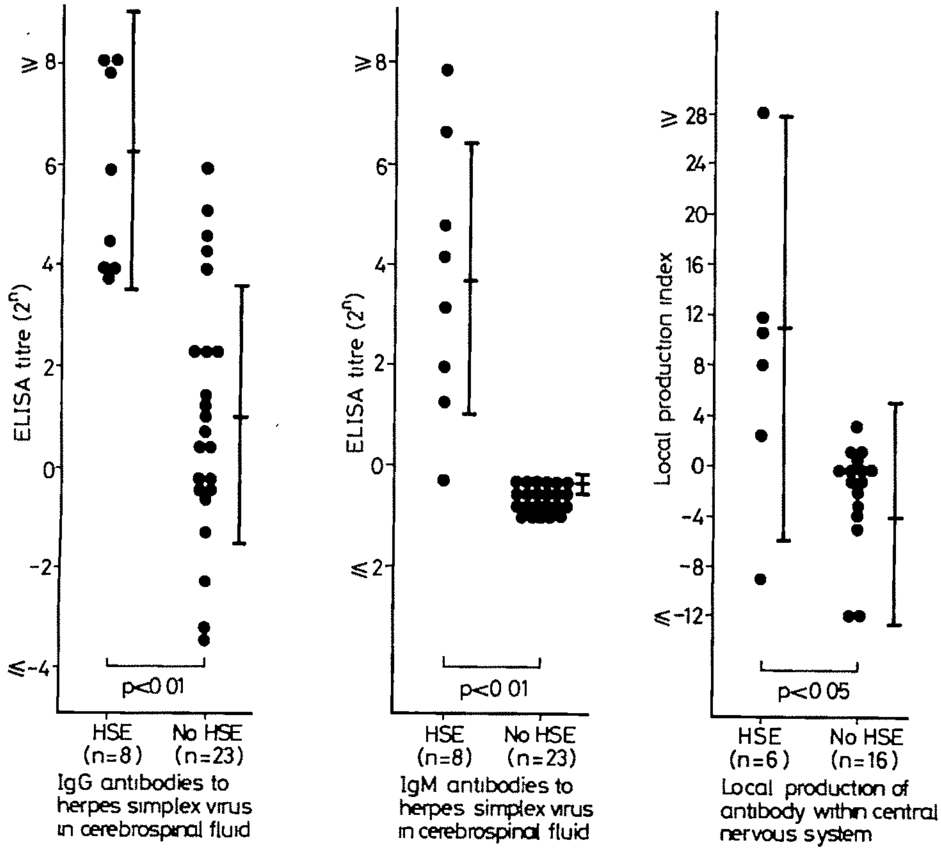

Figure *Comparisons of IgG antibodies and IgM antibodies to herpes simplex virus and local production of antibody with the central nervous system between patients with and patients without herpes simplex encephalitis (HSE). The vertical lines represent mean (SD).*

eight of the patients with herpes simplex encephalitis and five of those who did not have herpes simplex encephalitis were positive by the first criterion, indicating that escape of serum antibodies across the blood brain barrier can occur in some neurological illnesses. Seven of the eight patients with herpes simplex encephalitis and none of those who did not have herpes simplex encephalitis were positive by the second criterion. Four of the eight patients with herpes simplex encephalitis and none of those who did not have herpes simplex encephalitis were positive by the third criterion. The patients who were positive by more than two criteria all had herpes simplex encephalitis in retrospect (cases 1–8), and five (cases 16, 20, 21, 22, and 25) were diagnosed as not having had herpes simplex encephalitis because of the negative results using the second and third criteria. Thus all the cases of herpes simplex encephalitis were diagnosed and there were no false positive results using all three criteria in the acute phase of the illnesses. The mean period from the onset of herpes simplex encephalitis to diagnosis was 6·7 days (range 4 to 10 days).

Discussion

The early diagnosis of herpes simplex encephalitis is extremely important because prognosis depends on the patient's degree of consciousness when treatment starts.[1] Effective chemotherapy should therefore be started as soon as possible, before there has been any deterioration of consciousness.

Among the methods of early diagnosis, brain biopsy is one of the most accurate, but this may not be the first choice because of its risk, particularly in mild cases of herpes simplex encephalitis that recover without any specific treatment.[5] As the amount of intrathecal synthesis of antibodies is also large in such cases, the diagnosis by detection of antibodies to herpes simplex virus in the cerebrospinal fluid might be more applicable. Positive immunofluorescence to herpes simplex virus antigen

Table *Results of early diagnosis by the criteria described (see text)*

Case No	*Age (years)*	*IgG antibodies to HSV in cerebrospinal fluid*	*IgM antibodies to HSV in cerebrospinal fluid*	*Local production of antibody within central nervous system*	*Final diagnosis*
1	0	–	+	+	HSE
2	4	–	+	+	HSE
3	0	–	+		HSE
4	16	–	+		HSE
5	4	–	+		HSE
6	7	–		+	HSE
7	2	–	+	+	HSE
8	4	–	+		HSE
9	16				Encephalitis (entero)
10	7				Encephalitis (entero)
11	5				Encephalitis (entero)
12	7				VZVME
13	5				VZVME
14	2				Encephalitis (non-HSE)
15	11				Encephalitis (non-HSE)
16	12	–			Encephalitis (non-HSE)
17	11				Encephalitis (non-HSE)
18	2				Encephalitis (non-HSE)
19	4				Encephalitis (non-HSE)
20	6	–			Encephalitis (non-HSE)
21	13	–			Encephalitis (non-HSE)
22	10	–			Encephalitis (measles)
23	3				Encephalitis (measles)
24	1				Encephalitis (measles)
25	4	–			Encephalitis (measles)
26	5				Encephalitis (mumps)
27	0				Anoxic encephalopathy
28	9				SSPE
29	9				Guillain-Barré syndrome
30	7				Brain tumour
31	3				Brain abscess

HSE. Herpes simplex encephalitis; HSV herpes simplex virus, entero: meningoencephalitis caused by enteroviruses, VZVME. Varicella zoster virus meningoencephalitis; and SSPE subacute sclerosing panencephalitis in cerebrospinal fluid cells,[6] and detection of an early herpes simplex virus antigen in the cerebrospinal fluid may have a limited use.[7] Many reports[3] have shown that high titres of antibodies to herpes simplex virus in cerebrospinal fluid is characteristic of herpes simplex encephalitis, and measurement of these titres could be useful for the early diagnosis of herpes simplex encephalitis. It is important, however, to distinguish between the local production of antibodies to herpes simplex virus and those produced in the serum that cross the damaged blood brain barrier. To clarify this point, we calculated the local production index, which was based on the correction of antibody against control virus by the C:S ratio.

Klapper *et al*[8] reported that out of 10 patients with herpes simplex encephalitis tested within 10 days of the onset of their neurological illnesses, five had positive diagnostic indices by radioimmunoassay. Using our method, all patients with herpes simplex encephalitis could be diagnosed within 10 days of onset, and there were no false positive results. The mean time required for the diagnosis in our study was 6·7 days from the onset of herpes simplex encephalitis, which was shorter than in their report. It took only a few hours to measure antibodies by ELISA, so it might be more useful for rapid early diagnosis than the radioimmunoassay because of the simplicity of the methods.

In our study no patient without IgG antibodies to herpes simplex virus in the cerebrospinal fluid had herpes simplex encephalitis, but all patients who had IgM antibodies to herpes simplex virus in the cerebrospinal fluid had herpes simplex encephalitis. Patients who did not have IgM antibodies but did have IgG antibodies to herpes simplex virus could not be excluded from the herpes simplex encephalitis group on those criteria alone. They could, however, be diagnosed by using the third criterion; when the local production index was positive, they had herpes simplex encephalitis and when it was not, they did not. All 31 cases were diagnosed using this method in the acute phase. The sensitivities and specificities of our results were 100% (8 of 8) for herpes simplex encephalitis and 78·3% (18 of 23) for those that did not have herpes simplex encephalitis using the first criterion; 87·5% (7 of 8) and 100% (23 or 23) using the second criterion; and 50% (4 of 8) and 100% (23 of 23) using the third criterion. These figures improved to 100% (8 of 8) and 100% (23 of 23) when the criteria were combined. Both sensitivity and specificity improved remarkably when the third criterion was incorporated.

Kahlon *et al*[9] showed recently the intrathecal synthesis of antibody against the viral structural protein of herpes simplex virus in herpes simplex encephalitis by the immunoblotting method. They reported that antibodies in cerebrospinal fluid against the glycoprotein B in herpes simplex virus rose sooner than antibodies to the other viral proteins, probably because of the high immunogenicity of glycoprotein B. It might be possible to improve the sensitivity for detection of antibodies to herpes simplex virus by using purified glycoprotein B as an antigen.

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Diagnosis of brain death by transcranial Doppler sonography

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SUMMARY The blood flow velocities in the basal cerebral arteries can be recorded at any age by transcranial Doppler sonography. We examined nine children with either initial or developing clinical signs of brain death. Soon after successful resuscitation increased diastolic flow velocities indicated a probable decrease in cerebrovascular resistance; this was of no particular prognostic importance. As soon as there was a clinical deterioration, there was a reduction in flow velocities with retrograde flow during early diastole, probably due to an increase in cerebrovascular resistance; this indicated a doubtful prognosis. In eight of the nine children with clinical signs of brain death a typical reverberating flow pattern was found, which was characterised by a counterbalancing short forward flow in systole and a short retrograde flow in early diastole. This indicated arrest of cerebral blood flow. One newborn showed normal systolic and end diastolic flow velocities in the basal cerebral arteries for two days despite clinical and electroencephalographic signs of brain death. Shunting of blood through the circle of Willis without effective cerebral perfusion may explain this phenomenon. No patient had the typical reverberating flow pattern without being clinically brain dead. Transcranial Doppler sonography is a reliable technique, which can be used at the bedside for the confirmation or the exclusion of brain death in children in addition to the clinical examination.

Only modern techniques of intensive care have made the diagnosis of 'brain death' possible.[1] Brain death is the complete and irreversible cessation of brain function, even though the blood continues to circulate in the rest of the body. The death of the brain means the death of the person.[2] Clinical criteria for brain death in adults and children have been established by various committees.[2–5] In addition, confirmation of brain death by laboratory tests is often necessary. Four vessel arteriography,[6] radionuclide cerebral angiography,[7] Doppler sonography of the extracranial brain supplying arteries,[8] serial electroencephalograms, and brainstem auditory evoked potentials[9] have also been used. These techniques have, however, inherent problems that limit their application.

With transcranial Doppler sonography it is possible to record the flow velocities in the intracranial basal cerebral arteries at any age.[10] This technique is rapidly available, harmless, and reliable.[10 11] The aim of our study was to find out if in children it is possible to confirm the clinical diagnosis of brain death by showing cessation of intracranial forward blood flow with transcranial Doppler sonography.

Patients and methods

Between September 1985 and December 1987, 27 unconscious children (Glasgow coma scale <8) were examined. Nine patients (eight of them after successful resuscitation) presented the clinical signs of either initial or developing brain death. These were deep coma, no spontaneous respiration, and no brain stem reflexes (pupillary, oculocephalic, corneal, pharyngeal, tracheal, or trigeminal pain reaction). Drugs, hypothermia, and endocrine or metabolic causes for coma had been excluded. The ages and clinical diagnoses are shown in the table.

Transcranial Doppler sonography was carried out by an EME TC 2–64 system (EME, Uberlingen, West Germany) with a pulsed 2 MHz Doppler probe and an integrated fast Fourier real time frequency analyser (sliding average technique, 64 frequency points, 132 spectral lines). The supraclinoidal segments of both internal carotid arteries were inson-

Table *Patients with clinical signs of brain death*

Case No	*Age*	*Diagnosis*
1	12 years	Near drowning
2	12 years	Severe head injury
3	10 years	Brainstem aneurysm
4	7 years	Mucoviscidosis
5	5 years	Severe head injury
6	16 months	Obstructive apnoea
7	12 months	Sudden infant death syndrome
8	3 months	Sudden infant death syndrome
9	2 weeks	Complication of anaesthesia

ated by placing the Doppler probe on to the temporal bone between the lateral margin of the orbit and the ear, about 1 cm abvove the zygomatic arch. The ultrasonic beam was directed slightly forwards.[10 12] In infants, these vessels were found with the probe on the anterior fontanelle with the beam directed towards the angle of the lower jaw.[11] The basilar artery was insonated with the transducer in the midline of the neck and the ultrasonic beam directed through the foramen magnum. The measuring depth was adjusted to previously established age dependent values.[11] Systolic peak flow velocity, mean flow velocity (time mean of the maximum velocity envelope curve), and early and late diastolic peak flow velocity were calculated, and compared with the age dependent reference values.[11] Frequency to blood flow velocity conversions assumed an insonation angle of zero. In addition, the shape of the whole Doppler range during one cardiac cycle was analysed.

Arterial blood pressure was measured at the same time as the Doppler readings were taken. Carbon dioxide tension was measured either transcutaneously or from arterial blood samples.

Electroencephalograms were recorded with a Mingograf EEG 10 (Siemens, Erlangen, West Germany). Brainstem auditory evoked potentials were derived by a Tesy II device (Tönnies, Freiburg, West Germany). Real time cranial ultrasound through the anterior fontanelle was carried out with a Mark 100 (Advanced Technology Laboratories, Seattle, USA) with a short focused 5 MHz transducer. Four vessel arteriography was done by catheterisation under fluoroscopic control.

The study was approved by the hospital ethical committee.

Results

During all Doppler readings of this series the arterial blood pressure was within the normal range for age, and the transcutaneous or arterial carbon dioxide tensions were above 3·33 kPa.

After successful resuscitation transcranial Doppler sonography showed normal systolic peak flow velocities and increased end diastolic peak flow velocities in the basal cerebral arteries (fig 1a). At the same time as the clinical deterioration occurred, but before the clinical signs of brain death were obvious, zero or even retrograde early diastolic peak flow velocities and anterograde end diastolic peak flow velocities were recorded (fig 1b). Finally, a characteristic reverberating flow pattern with a short and low forward flow in systole and a counterbalancing retrograde flow in early diastole was seen in both internal carotid arteries and in the basilar artery (fig 1c). In case 5 this pattern appeared in the internal carotid arteries some hours earlier than in the basilar artery. It was also recorded in cases 1–8. All patients died within 24 hours or on discontinuation

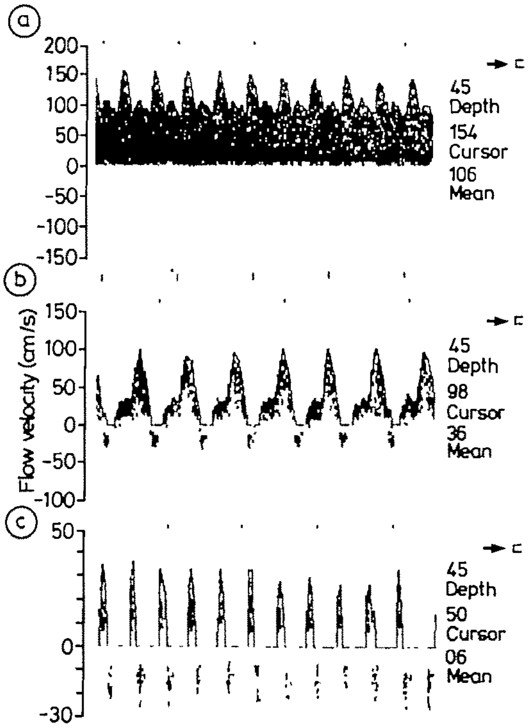

Fig 1 *Progression to brain death. Transcranial Doppler sonography of left internal carotid artery. Depth= measuring depth in mm, cursor=systolic peak flow velocity, and mean=time mean of the maximum velocity envelope curve The arrow to the right indicates that a flow towards the probe is shown above the zero line. (a)—Three hours after resuscitation, (b)—24 hours after resuscitation, and (c)—with clinical signs of brain death*

of mechanical ventilation. In case 9 a flow pattern as shown in fig 1a indicated the persistence of an intracranial circulation for two days, despite clinical and electroencephalographic evidence of brain death. Another infant presented with deep coma (Glasgow coma scale 5) and severe brain oedema shown on computed tomography after shaking trauma due to child abuse. At the same time as the clinical deterioration occurred, there was a reduction in the diastolic flow velocities in both internal carotid arteries, and an early diastolic retrograde flow was seen in the basilar artery (fig 2) The flow velocities increased again within 24 hours when there was a slight clinical improvement. This child survived in a vegetative state

The electroencephalograms carried out in seven patients (cases 1, 2, 3, 4, 6, 7, and 9) showed isoelectric tracings either initially or later on. The intracranial components of brainstem auditory evoked potentials were derived in three patients. They were decreasing in case 1 and were already absent in the first recordings of cases 7 and 9. Real time cranial ultrasound was possible in three infants and showed diffusely increased echogenicity of the brain parenchyma. The pulsations of the intracranial arteries were absent in cases 7 and 8, and in case 9 they persisted in the basal cerebral arteries.

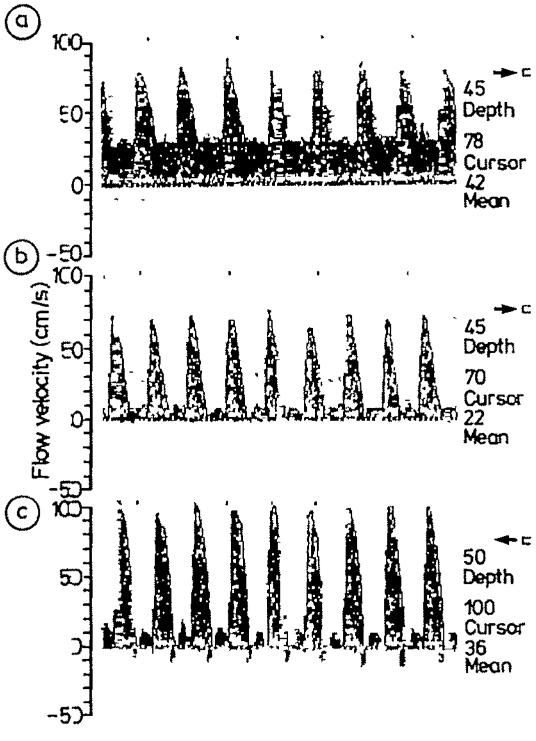

Fig 2 *Cerebral shaking trauma—transcranial Doppler sonography. Depth=measuring depth in mm, cursor=systolic peak flow velocity, and mean=time mean of the maximum velocity curve. The arrow towards the left indicates that a flow away from the Doppler probe is shown above the zero line. (a)—Left internal carotid artery on day 4 after trauma, (b)—left internal carotid artery on day five, and (c)—basilar artery on day five.*

Cerebral arteriography was carried out in case 3 after clinical, electroencephalographic, and Doppler sonographic confirmation of brain death before organs were removed for transplantation There was no flow in either the two internal carotid or the vertebral arteries.

Examination at necropsy showed severe brain oedema (cases 2, 6, 7, and 8) with superior and inferior herniation (case 6), hypoxic/ischaemic neuronal damage (case 8), or liquification of the brain (cases 1 and 9).

Discussion

Though many authors accept the diagnosis of brain death by clinical criteria alone,[3 4 5] additional laboratory tests are often used for confirmation or objective assessment. As these tests monitor either the circulation or the electrical activity of the brain their results are not always comparable. We will discuss only some tests of cerebral circulation.

Four vessel arteriography has shown arrest of cerebral blood flow and a characteristic to and fro movement of the blood below the base of the skull in the arteries supplying the brain.[6] Because the injected contrast medium may aggravate pre-existing brain oedema we use this technique only for confirmation and assessment before the removal of organs for transplantation when there is no doubt about the diagnosis of brain death. Radionuclide techniques are less invasive and give only small doses of radiation. They are less reliable, but can be used for diagnosing brain death.[7] Doppler sonography has no known side effects and is not invasive. The Doppler technique records flow velocities in arteries supplying the brain, but cannot quantitatively determine cerebral blood flow. This, however, is not necessary for the diagnosis of brain death in which the cessation of intracranial forward blood flow alone has to be shown.

It has been shown that increased intracranial pressure may influence the Doppler velocity profiles in the intracranial arteries in infancy.[13 14] In brain death different Doppler profiles have been recorded from different arteries. In adult brain death a to and fro movement and escape of carotid arterial blood externally was seen.[8] In children with brain death there is a sharp systolic peak followed by a negative deflection, again a forward flow in early to mid diastole, then almost no flow at the end diastole in the common carotid artery.[7] During the progression to brain death in neonates, there is a sequence of loss of diastolic flow, appearance of retrograde flow during diastole, diminution in systolic flow, and ultimately no detectable flow in the anterior cerebral artery despite considerable flow in the common carotid artery.[15]

Only transcranial Doppler sonography, which combines a low emitting frequency with the pulsed Doppler technique, can determine the intracranial blood flow velocities at any age. Characteristic reverberating Doppler profiles were recorded in the basal cerebral arteries of adults with brain death: brief systolic orthograde and early diastolic retrograde movements indicating net zero flow.[12] In only a few adults the sound beam is unable to penetrate the skull,[10–12] and then Doppler signals from the intracranial arteries cannot be recorded, and the diagnosis of brain death is impossible.

We present the first results of transcranial Doppler sonography in children with clinical signs of brain death initially or later on. The increased end diastolic flow velocities soon after resuscitation probably indicate the vasogenic phase of cerebral oedema that results from a decrease of the cerebrovascular resistance caused by vasodilation of the peripheral cerebral vessels. This is obviously a reversible phenomenon that we also saw in patients who had favourable outcomes.

We speculate that the prognostically doubtful pattern of reduced systolic flow velocities, retrograde flow velocities in early diastole, and then anterograde end distolic flow velocities, is caused by an increase of the cerebrovascular resistance. This could be a result of increasing brain oedema and the swelling of the endothelium of the small cerebral vessels.[8] Changes in the compliance of the arteries supplying the brain may alter pulse wave reflexions from distally occluded arteries. The sharp Doppler signals with forward flow in systole and reversed flow in diastole are probably caused by the compliance of the basal cerebral arteries, and indicate the cessation of intracranial net forward blood flow in brain death. We never obtained the flow pattern shown in fig 1c in children who were not clinically brain dead. The 18 surviving children with temporary deep unconsciousness always showed anterograde pandiastolic flow; the flow pattern of fig 1a was often seen. The typical reverberating flow pattern in both internal carotid and the basilar artery is therefore highly specific for brain death, and we believe it can serve as a confirmatory test in children as well as in adults.

Our findings with transcranial Doppler sonography during progression towards brain death are similar to the results obtained from the common carotid artery in children who were brain dead.[7] In contrast to that study, we found that an early diastolic retrograde flow in the basal cerebral arteries may indicate imminent brain death, but patients may also survive with severe deficits. In some cases, arrest of intracranial flow may not occur exactly at the same time in different basal cerebral arteries. It may also occur in severe infratentorial injuries. Under such circumstances clinical signs and brainstem evoked potentials may indicate brain death, while Doppler sonography still shows continuing blood flow in the arteries supplying the supratentorial parts of the brain. Further study of these problems is required.

On the other hand, in newborn infants flow velocities appropriate for age may persist through the basal cerebral arteries for some days in spite of brain death proved by clinical signs, electroencephalography, and necropsy. The flow velocities may not correspond to an appropriate cerebral blood flow because the diameter of the basal cerebral arteries is unknown. The flow may be decreased due to endothelial swelling, but the Doppler readings indicate a different pathophysiological process leading to brain death in this age group. We speculate that the blood is shunted through the circle of Willis and into extracranial arteries without cerebral perfusion. This phenomenon has been discovered by angiography in children who are brain dead.[6] The persistent pulsations of the basal cerebral arteries alone in cranial ultrasound further support this. Therefore the diagnosis of brain death by Doppler sonography may be difficult or impossible in neonates.[7 16] There are also problems of diagnosing brain death in neonates that are associated with the clinical signs,[2] the electroencephalogram,[9] and brainstem evoked potentials.[17]

The advantage of transcranial Doppler sonography for examining intracranial arteries in cases of suspected brain death when compared with Doppler techniques that only record the flow in the extracranial arteries supplying the brain is obvious; only transcranial Doppler sonography can record intracranial flow velocities at any age. Like other Doppler techniques it is dependent on the experience of the examiner, but the technique is comparatively easy to perform. It is not affected by artefacts or drugs that may make the evaluation of techniques that record the electrical activities of the brain on intensive care units difficult or even impossible. Finally, the rapid availability of the instrument and the speed with which the results are obtained makes it the preferred method for use at the bedside for excluding or confirming brain death in childhood after the clinical examination.

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Deliberate self poisoning in adolescents

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SUMMARY A retrospective study of 90 adolescents admitted to a district general hospital after deliberate drug overdoses was carried out. Underlying risk factors, the inpatient assessment, and the initial management offered to each patient were recorded. The longer term outcomes were assessed, with particular emphasis on psychiatric and related disorders. Many had underlying family problems; the parents of nearly half the patients were separated or divorced, and over half the families had already been seen by the social services or at the child guidance clinic. Three quarters of the patients had psychiatric assessments during admission, and of these 59 (66%) were referred for further psychiatric treatment. Of these over half withdrew from treatment. Eleven (12%) of the children took a further drug overdose. This study emphasises the need for psychiatric assessment and treatment in these children, but the results suggest that the success of management is limited by poor patient compliance.

The number of children under the age of 16 years admitted to hospital each year after attempts at deliberate self poisoning has been increasing over the past 20 to 30 years.[1 2] Self poisoning is far more common than self injury in attempted suicides in this age group.[1] Young people who take overdoses of drugs share various background characteristics including broken homes (through divorce, separation, or death of parents), parental psychiatric disturbance (including suicidal behaviour), and past histories of child abuse. Events immediately preceding suicide attempts include quarrels with parents or boy or girlfriends (often after long standing difficulties in their relationships with their parents), and social isolation.[1-4] Only a few young people with parasuicidal behaviour have a definite psychiatric illness, usually depression, but a considerable number are probably psychologically disturbed.[5]

In 1982 the Royal College of Psychiatrists published guidelines for the management of parasuicide in young people under the age of 16 years.[6] These stated that all patients in this group seen after an overdose should be admitted to hospital, preferably to a paediatric ward. They should be treated there for any effects of drug toxicity, and they should remain in hospital until an assessment could be made by a member of the child psychiatric team. The guidelines recommended that in areas with limited resources the child should be kept in hospital for a few days, even if medically fit for discharge, in order for such an assessment to be made.

St Helier Hospital is a district general hospital outside London. Within the district there are two child guidance clinics, and there is a department of child psychiatry at a nearby children's hospital. During much of the study period, however, there were no child psychiatry sessions at the district general hospital. An informal weekly paediatric and psychiatric liaison meeting was initiated during the study period, and children are now seen in the ward by request. In addition there is a regional adolescent unit to which referrals may be made.

The aim of this study was to look into the background characteristics of each patient admitted to the paediatric ward after a deliberate drug overdose, and to assess the factors that precipitated the overdose. Its other aim was to look at the assessment each patient received in hospital, the subsequent follow up, and whether or not the patient complied with this treatment.

Patients and methods

Between 1 January 1980 and 31 December 1985 a total of 90 children were admitted to the general paediatric ward at St Helier Hospital after deliberate attempts at self poisoning. Information about these patients was initially obtained by examining the hospital case notes. Details noted about each patient included sex, age at the time of the overdose, and particulars of the family and social background. Whatever precipitated the overdose was also noted and the drug (or drugs) taken.

Details of the management of each child in hospital were obtained from the case notes, which also gave the initial follow up plan. Further information on each patient was then obtained by contacting the various agencies concerned: the child guidance clinics, the regional adolescent unit, the social services, the general practitioners, or other hospitals. It was then possible to ascertain whether each patient had attended for their follow up appointments as arranged, whether they completed their treatment, or whether a referral to a further agency was necessary.

Results

Ninety children were admitted during the study period, with a mean admission rate of 15 patients a year (range 6–20). The lowest admission rate was six patients in 1980, increasing to 20 in 1982; this increase was subsequently sustained. The ratio of boys to girls was 1:8. The average age of the whole group was 14·5 years (range 10·4–16·6 years). The figure shows the age and sex distribution of the patients; only one was under the age of 12 years at the time of admission. She was the sibling of another child who had been admitted earlier in the same year after taking an overdose, and came from a disrupted family background.

Table 1 shows the details of the family and social background of the patients. Of the 90 children, 39 (43%) came from homes where the parents were divorced or separated, and in 49 cases (54%) the patient or the family, or both, had previously been referred to, or were currently under follow up, either by the social services or the child guidance service. In only three cases was a clear history of child abuse obtained: one of the children had been sexually abused by her stepfather for some years, and another girl had been sexually abused by an uncle. The third was a case of physical abuse by the child's father.

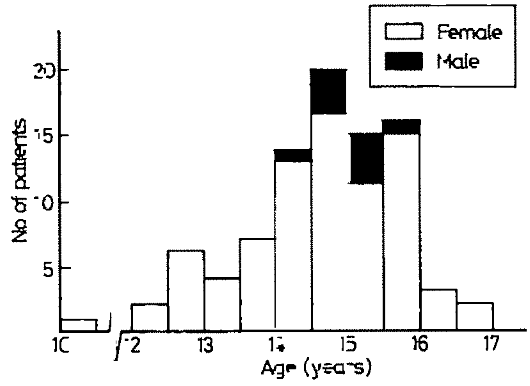

Figure *Age and sex distribution of patients*

Table 1 *Background of the children*

	No (%)
Parents divorced or separated	39 (43)
Family seen at child guidance clinic	27 (30)
Family seen by social services	22 (24)
Subject in childrens' home	6 (7)
History of child abuse	3 (3)
Subject adopted	1 (1)

The drugs taken most commonly were paracetamol (51%) and salicylates (30%). Twenty three patients (26%) took either tranquillisers or antidepressants, which in most cases had been prescribed for another member of the household. Only three of the children took alcohol with the overdose.

There were no deaths in the study group: only one patient (who had taken amphetamines) was ill enough to require admission to the intensive care unit, and only 13 (14%) required specific medical treatment as a result of their overdose. The remainder were kept under observation but they remained satisfactory with no untoward effects, and in those in whom serum concentrations of the drugs were measurable, they were below the toxic range.

The specific factors precipitating the overdoses are shown in table 2. The single most common risk factor was a problem within the family—in particular, difficulties in the relationships between the children and either parent (or step-parent). In 40 of the 90 (44%) there were several precipitating factors—for example, difficulties at school for a child who was also experiencing problems with family relationships.

Sixty six (73%) of the children were seen by a member of the child psychiatric team during their hospital admissions: this was either the consultant in child psychiatry (or, less commonly, a senior registrar or registrar working with him), or a psychotherapist. Sixteen patients (18%) were seen

Table 2 *Reason for overdose*

	No (%)
More than one reason	40 (45)
Family problems	29 (32)
Row with boy or girlfriend	9 (10)
Bereavement	4 (4)
Problems at school	3 (3)
Physical illness	3 (3)
Prank	3 (3)

by one of the hospital social workers attached to the paediatric department who were accustomed to dealing with such problems. Of the remaining eight patients, five were seen by a consultant paediatrician who felt that no further intervention was required, in two cases the parents refused help and took the child's discharge against medical advice, and the remaining patient was already being treated for depression by a general practitioner in another health district who arranged for her to be seen by a psychiatrist in that area The length of stay in hospital varied between one and 16 days: one day, 25 patients; two days, 24; three days, five; four days, six; five days, seven; six days, one; seven days, five; eight days, four; nine days, three; 10 days, three; 11 days, one; 12 days, two; 13 days, one; 14 days, two; 15 days, none; and 16 days, one. Only one patient was kept in hospital because of a medical problem: in all the others the time spent in hospital was dependent on a satisfactory psychiatric assessment, which sometimes concerned several agencies.

As a result of the initial consultations in hospital, 59 (66%) of the children were referred for further psychiatric help. Of these 46 were seen at the child guidance clinic, 12 at the adolescent unit, and one by a psychiatrist in an adult unit. A further 10 children were referred to area social services for follow up (table 3). Seven patients refused follow up; these included the two patients already mentioned whose parents took their discharge before an assessment could be made, and the other five were seen by a member of the psychiatric team or a social worker while in hospital but declined the follow up offered. Ten patients had no specific follow up, six because the psychiatric team thought it was unnecessary, but four unfortunately do not seem to have been referred.

The outcome of the initial psychiatric referrals is shown in table 4. Only 15 of the 59 patients referred for further help (25%) actually completed their treatment to the point of being discharged. Three required inpatient treatment and nine were subsequently referred elsewhere for further help. In the latter group, four were referred to the adolescent unit, in which only one patient actually completed her treatment; three patients were subject to care orders, one was placed in a residential hostel, and two were referred to an educational psychologist. In all, 35 of the 59 (59%) did not complete the suggested course of treatment. Failure to cooperate with treatment did not appear to be associated with the reason for taking the overdose.

Table 3 *Agency to which child was initially referred*

	No (%)
Child guidance clinic	46 (52)
Adolescent unit	12 (13)
Psychiatrist	1 (1)
Area social worker	10 (11)
Special school	3 (3)
Place of safety	1 (1)
Refused any follow up	7 (8)
Nil	10 (11)

Table 4 *Outcome of initial psychiatric referral*

	No (%)
Did not attend	10 (17)
Initally attended then did not	22 (37)
Completed treatment	15 (25)
Inpatient treatment	3 (6)
Secondary referral	9 (15)

Finally, certain other problems were identified in the overall study group of 90. Five (6%) were definitely known to be drug abusers at the time of the study, and four (4%) were referred back to the psychiatric services at a later date with new problems (not as a result of further suicide attempts).

Eleven (12%) of the study group were known to have taken a further overdose at the time of the study: one had done so within six months of the initial presentation, and a further five within one year. The other five had presented again as a result of deliberate self poisoning between 12 and 26 months of the first admission. Five of this group of 11 patients had withdrawn from treatment by the time they took their second overdose.

Discussion

Children aged 16 years and under who deliberately take drug overdoses make up an appreciable number of the acute admissions to paediatric wards, and this is a problem which seems likely to continue.[7] It is therefore essential that in addition to attempting to identify the 'at risk' groups, attention is paid to subsequent management to lessen the possibility of their repeating the suicide attempt. In this study there was a pronounced increase in the annual admission rate between 1980 and 1982 which was then sustained. This increase is unlikely to be a chance finding; it probably reflects a combination of a genuine increase in the incidence of self poisoning in adolescents, and an increased awareness of the problem and how it is best managed.

Theoretically, all children aged 16 years and younger who are seen in the accident and emergency department of this hospital after deliberate drug overdoses are now referred to the paediatricians for admission and further assessment, whereas previously those who had taken comparatively trivial overdoses and were clinically well would have been discharged with no further assessment or follow up

The results of this study confirmed some of the characteristics of children taking overdoses that have previously been recorded. Hawton *et al* found a female:male ratio of 9:1,[2] and White[1] and Rohn *et al*[3] found 82% and 75% of girls, respectively. Only one of the patients in this group was under the age of 12 years. Neither Hawton *et al* nor White have any children under 13 years of age in their studies, although Rohn *et al* gave an age range of 7–19 years. Lumsden Walker had five children aged 12 years or less in his series of 50 consecutive admissions [4]

Details of the family and social background, and also of the immediately precipitating factors of the overdose were similar to the findings of others.[1–3] Loss of a parent through separation or divorce was a common feature, as were relationship problems with parents or step-parents.

The number of children who were definitely victims of child abuse is almost certainly an underestimate; perhaps the increased awareness of this problem will lead to more cases being identified in the future.

School problems were not a major precipitating factor, contrary to reports of other authors[4]; in only three of these cases were worries at school deemed to be the single factor preceding the suicide attempt.

As in this study, Hawton *et al* found that two thirds of his group took either paracetamol or salicylates[2]. He also found that these drugs were taken more commonly by the group less than 15 years old than by the 16–18 year olds. He also found that only a small number consumed alcohol. Both paracetamol and aspirin can be readily bought from chemists and supermarkets, or are in the family drug cabinet, yet in toxic doses both are potentially lethal. Fortunately most of the patients took only small quantities of the drugs, with only 14% of the whole group requiring specific medical treatment for poisoning. It seems that most of these children do not have serious suicidal thoughts, but their actions in taking an overdose are impulsive It is unlikely that many, if any, realise the potential hazards of taking an excessive number of what they probably regard as comparatively harmless drugs, and education has therefore an important part to play in management

An appreciable number of children stayed in hospital for an unacceptably long time. In our area this is no longer such a problem because of improvements in the paediatric/psychiatric liaison in the past few years, but in areas with limited resources (particularly in the form of child psychiatric services) it is likely that children are either kept in hospital for longer than necessary, or are discharged with an outpatient appointment to be seen by a psychiatrist but with no acute assessment being made at the time of the overdose. In both instances by the time the child is seen the crisis is over. The weekly paediatric/psychiatric liaison meeting at this hospital was initiated at the request of the paediatricians at a time when there was no immediate prospect of an increase in the number of child psychiatry sessions in the district This gave the paediatricians the opportunity to discuss cases, including those admitted after deliberate self poisoning, with their psychiatric colleagues. Since this study was completed, more child psychiatry sessions have been allocated at the district general hospital.

This leads on to another important point—the finding that more than half of the patients referred for further psychiatric help withdrew from treatment. This confirms the finding of White.[1] One way in which compliance may be improved is if the time between admission and the psychiatric assessment is shortened, and if the liaison between the various agencies concerned in making these assessments is speeded up. Newson-Smith and Hirsch assessed the ability of trained social workers to carry out initial assessments on patients who had attempted suicide and suggested that in hospitals where social workers were more readily available than psychiatrists, they should undertake some of these assessments.[8]

Concerning longer term problems, the figure of 6% who were known to be drug abusers at the time of this study is (like the previously quoted figure for child abuse) almost certainly an underestimate as there are likely to be several more who are not registered drug abusers. The figure of 4% who were referred for psychiatric help at a later date, however, is probably fairly accurate as information about this is more readily obtainable. This bears out the hypothesis that this particular group of children are more psychologically than psychiatrically disturbed

The number of children who repeated the suicide attempt (12%) is similar to that found in other studies White[1] followed up his patients for one year and in this time 12% committed further acts of self harm. Similarly, Hawton *et al*[2] found that 14% of their group repeated their self poisoning attempts within one year (10% of these within the first three months). The fact that nearly half of those in this study who repeated the attempt had withdrawn from treatment emphasises the point that compliance is a serious obstacle in trying to help these young people .

Finally, because this was a retrospective study, it was not possible to examine directly the motivation behind the suicide attempts This was studied by Hawton *et al* and one of the conclusions from their study was that adolescents rarely took overdoses to get professional help, and this may partly explain the poor compliance with treatment.[9] They suggested that rather than developing specialised agencies to help adolescents once they have considered taking an overdose, one should seek to modify their attitudes both to self poisoning and to seeking help at an early stage of their problems—not after a crisis develops. This could be achieved through discussion in schools, and possibly by education in the media. Taylor[10] puts forward a similar view in favour of preventive counselling services, which are not just available to those who are suicidal.

In conclusion, those children and adolescents who are admitted to hospital following deliberate drug overdoses share a number of clearly identifiable background characteristics. Guidelines have been laid down for the management of these patients from the time they present to the accident and emergency department, but follow up suggests that however well these guidelines are adhered to, the ultimate success of treatment is largely limited by poor patient compliance. Education and preventive counselling services should be expanded to help those young people who are at risk.

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Atlantoaxial instability and abnormalities of the odontoid in Down's syndrome

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SUMMARY Radiography of the lateral neck was performed on all children with Down's syndrome aged 4–15 in the Southern Derbyshire health district (n=67) and a random selection of adults (n=94). Atlantoaxial instability, defined as a gap of over 4 mm, was present in seven (10%) children and two (2%) adults. Odontoid hypoplasia, defined as an odontoid peg two standard deviations below the mean in an age matched population, was present in 15 (22%) children and 14 (15%) adults, with accessory odontoid ossicles present in two (2%) and two (3%) respectively. No one was found to have symptoms or clinical signs of spinal cord compression. Atlantoaxial instability was therefore found to be commoner in children than adults. Different programmes of management are suggested, in terms of regular clinical examination for signs and symptoms and by radiographic screening. Particular care should be taken with those who have both atlantoaxial instability and odontoid hypoplasia or accessory ossicles as they are at particular risk of spinal cord damage.

Interest in upper cervical instability in Down's syndrome has recently been renewed after the recommendation by the Committee on Sports of the American Academy of Pediatrics relating to participation in sporting activities.[1] The Committee recommends preparticipation radiographs of the cervical spine in flexion, extension, and neutral, with attention being directed to the atlantoaxial region in order to prevent serious damage to the spinal cord. Similar recommendations have been made in Britain by the Department of Health and Social Security (DHSS)[2] and Mencap.[3]

Abnormalities of the upper cervical spine in Down's syndrome have been recognised since the original work of Tishler and Martel in 1965.[4] There is a reported incidence of atlantoaxial instability of between 9·5 and 27%.[5-7] People with Down's syndrome also have an increased incidence of abnormalities of the odontoid peg[6] and this may predispose to damage if they also have atlantoaxial instability.[8] We found 13 cases of symptomatic atlantoaxial instability in Down's syndrome reported in the literature in which features of the odontoid peg were specifically mentioned. All 13 had accessory ossicles and eight had coexistent odontoid hypoplasia, although the size of the odontoid peg was not mentioned in the other five.[8-17]

Unfortunately, surveys of atlantoaxial instability in Down's syndrome have generally been unable to comment on coexistent odontoid hypoplasia because of the lack of normative data for the growth of the odontoid peg during childhood. Some surveys have also reported atlanto-occipital instability which may lead to symptoms.[12 18 19] We report the only United Kingdom survey of radiographic screening in children and adults with Down's syndrome. Particular attention was paid to the presence of odontoid hypoplasia, using criteria for hypoplasia established in a parallel examination of cervical radiography in 500 normal children.[20]

Subjects and methods

Radiographs of the cervical spine were performed in all children in the Southern Derbyshire health district between the ages of 4 and 15 (n=67) and a random number of adults with Down's syndrome (n=94). The adults included 60 from adult training centres and 35 from the district long stay hospital. Radiographs were taken of the lateral cervical spine in flexion, extension, and neutral, at a film focus distance of 200 cm, as described by Clark.[21] All films were reviewed by two of the authors (SE and RAJW) and assessed for (1) atlantoaxial instability, (2) odontoid hypoplasia and accessory ossicles (os odontoideum and os terminale), and (3) atlanto-occipital instability. One adult refused to have a radiograph taken and was excluded from the results.

(1) Atlantoaxial instability was assessed by measuring the distance between the posterior-inferior aspect of the anterior arch of the atlas and the nearest adjacent surface of the odontoid process (z, fig 1). Measurements over 4 mm were taken as abnormal.[22]

(2) The hypoplastic odontoid has loosely been defined as an odontoid not reaching the upper edge of the anterior arch of the atlas.[23] We have recently found, however, that this is often a normal finding in children up to the age of about 9.[20] We assessed the height of the odontoid using the method described by McManners, measuring from the tip of the odontoid process to the superior aspect of the articular facets of C2 (y, fig 1).[24] In addition, we measured the distance from the tip of the odontoid process to the superior edge of the anterior arch of the atlas, which we termed the odontoid 'deficiency' (x, fig 1). The latter measurement must be taken (from a lateral radiograph) in the neutral postion.[23] Measurements of odontoid hypoplasia and deficiency were compared with measurements obtained in 500 age matched individuals up to the age of 20.[20]

(3) Atlanto-occipital instability was assessed by the method of El Khoury *et al.*[19] In normal people, the odontoid lies directly beneath the basion and this does not change with neck movement. This is not the case, however, when atlantoaxial instability occurs and the atlanto-occipital distance is better measured by the distance between the anterior arch of the atlas and the basion.

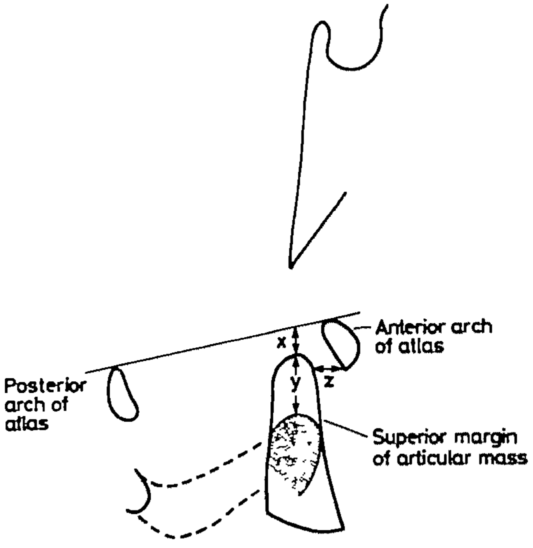

Fig 1 *Parameters measured in assessment of the atlantoaxial region. x=odontoid deficiency, y=odontoid height; and z=atlantoaxial gap*

In this study we considered adults to be those over the age of 15 years. Growth of the odontoid peg may be delayed in Down's syndrome during childhood because of bony immaturity, however, and we assessed normal adult values from those over the age of 19 years: these were very similar to adult values in the series of McManners.[24]

All patients under the age of 15 were seen by a clinician (RM) who checked for signs and symptoms of spinal cord compression. Those over the age of 15 were only seen by a clinician if atlantoaxial instability was found on the radiograph.

Statistical analysis of the results was performed by the Student's *t* test.

Results

Details of the atlantoaxial gap and the incidence of atlantoaxial instability in males and females above and below the age of 15 is given in table 1. Atlantoaxial instability was present in no children out of 11 under the age of 5, in five children out of 30 (17%) between 5 and 9, and two children out of 26 (8%) between 10 and 14 years. The incidence of odontoid hypoplasia, odontoid deficiency, and accessory ossicles is given in table 2.

Maximal atlantoaxial instability was always shown on the flexion film. In extension, the gap tended to decrease and the odontoid peg was not shown as well as on the neutral film. The size of the odontoid peg in our patients with Down's syndrome was

Table 1 *Atlantoaxial gap and incidence of atlantoaxial instability in Down's syndrome*

	Mean atlantoaxial gap (mm) (SD)	*No (%) with atlantoaxial instability*
	<15 years	
Male (n=28)	2·9 (1·3)	4 (14)
Female (n=39)	2·8 (1·2)	3 (8)
Total (n=67)	2·9 (1·2)*	7 (10)*
	≥15 years	
Male (n=51)	2·1 (1·8)	1 (2)
Female (n=43)	1·8 (0·9)	1 (2)
Total (n=94)	1·9 (1·5)*	2 (2)*

*Significant difference, p<0·05

compared with the peg size for the same age range in normals (shown in fig 2). Although there was a tendency for the peg to be generally smaller in Down's syndrome, this only achieved significance in the adult group.

Measurements of the odontoid deficiency in people with Down's syndrome was compared with normal controls (fig 3). Again, there was a tendency for a greater odontoid deficiency in Down's syndrome but this was only significant in the adults.

One child had appreciable atlantoaxial instability and odontoid hypoplasia. One adult had appreciable atlantoaxial instability together with a hypoplastic peg and os odontoideum. There was poor correlation between odontoid hypoplasia and significant odontoid deficiency; 29 people had odontoid hypoplasia but only seven had odontoid deficiency and six others had odontoid deficiency alone. Four patients had accessory ossicles, one of whom had odontoid hypoplasia.

No patients with atlantoaxial instability had signs or symptoms of spinal cord compression.

Table 2 *Problems of the odontoid peg in Down's syndrome*

	No (%) with odontoid hypoplasia	*No (%) with significant deficiency*	*No (%) with accessory ossicles*
	<19 years		
Males (n=39)	6 (15)	6 (15)	1 (2)
Females (n=51)	9 (17)	3 (5)	1 (3)
Total (n=90)	15 (17)	9 (10)	2 (2)
	≥19 years		
Males (n=40)	5 (13)	2 (5)	1 (2)
Females (n=31)	9 (29)	2 (5)	1 (2)
Total (n=71)	14 (20)	4 (5)	2 (3)

There were no significant differences

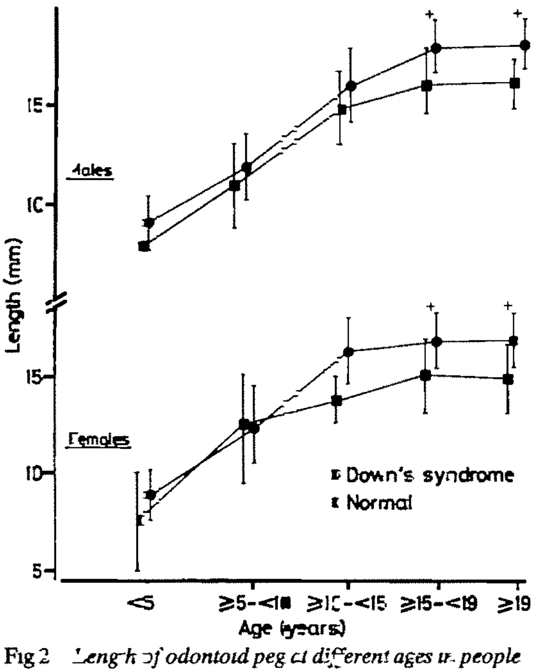

Fig 2 *Length of odontoid peg at different ages in people with Down's syndrome and in normal controls* +=*Significant difference, p<0·05.*

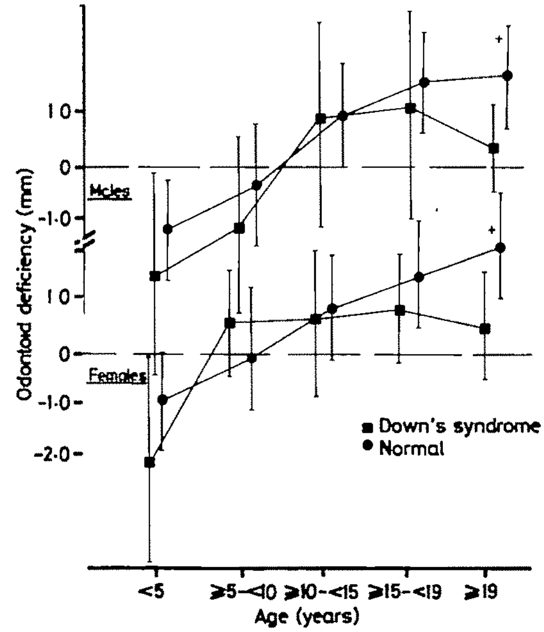

Fig 3 *Odontoid deficiency at different ages in people with Down's syndrome and in normal controls.* +=*Significant difference, p<0·05.*

Discussion

In people under the age of 15 we found an incidence of atlantoaxial instability of 10%, taking the upper limit of normal as 4 mm.[22] This was low compared with other studies, which indicated frequencies of 9·5–27% with 4–5 mm as the upper limit of normal.[5-7] For those people over the age of 15, we found an incidence of 2% with atlantoaxial instability using the same criteria. This figure is again low in comparison with the main study in adults, showing atlantoaxial instability in 10% of adults with a gap over 5 mm.[25] We feel the major reason for finding a low incidence of atlantoaxial instability was because we did not encourage hyperflexion of the neck, which is used in some studies to maximise the atlantoaxial gap. We considered this could be potentially dangerous and instead we simply asked the patients to flex their necks as much as was comfortable. Any difference between studies of the object-tube distance in taking the radiographs would be insignificant. Our patients were predominantly living in the community and included a wide range of all types of people with Down's syndrome. Many of the American series studied only institutionalised patients who could be expected to be in general more retarded with a possibily higher incidence of atlantoaxial instability

In our study an extension film was found to be unnecessary in screening the neck in Down's syndrome, one film in flexion indicating the maximal atlantoaxial gap and another in neutral allowed accurate visualisation of the odontoid peg. Recently Pueschel, however, reported a series in which up to 25% of people with atlantoaxial instability would have been missed if an extension film was excluded.[26]

Our study concerned a large group of people with Down's syndrome of all ages and indicated that the mean atlantoaxial gap is wider in young people compared with adults and that a greater proportion of young people have significant atlantoaxial subluxation. Laxity of the transverse ligament of the atlas predisposes to atlantoaxial instability, and this correlates with the degree of ligamentous laxity present in other joints in children with Down's syndrome.[6] Children also suffer from upper respiratory infections and trauma, both of which may cause atlantoaxial instability.[14 16 27]

There could be a greater degree of ligamentous laxity in adults because of degeneration of the transverse ligament, which like other aging processes, may occur faster in Down's syndrome. Different pathological processes may therefore be responsible for atlantoaxial instability in children and adults and occur in different people. In the only published longitudinal study of atlantoaxial instability in Down's syndrome radiographs were taken in 32 patients, 13 years apart.[10] One person had atlantoaxial instability initially but this disappeared, seven others originally had normal necks but later developed atlantoaxial instability.

We found that the odontoid peg was generally smaller in children and adults with Down's syndrome compared with normals. This is probably mainly because of the smaller stature in Down's syndrome, together with delayed growth of the peg in children due to their skeletal immaturity The odontoid peg does appear to be proportionally smaller in Down's syndrome as the odontoid deficiency is greater in Down's syndrome, but this was only significant in the adult group. Nevertheless, there is poor correlation between odontoid hypoplasia and odontoid deficiency and it is unclear which measurement of the odontoid peg is of most clinical importance. We prefer the measurement of odontoid hypoplasia that is used in other series—that is, odontoid height; we found that 17% of children had odontoid hypoplasia, that is two standard deviations below the mean for an age matched normal population. This compared with 6% in another series,[6] although the criteria were not mentioned. A total of 20% of adults in our series also had odontoid hypoplasia, two standard deviations below the mean.

We did not find any correlation between odontoid hypoplasia and atlantoaxial instability. Only one child had these conditions together (1·5%) and one adult had both conditions with an accessory os odontoideum (1%). Previous reports suggest that these people are at particular risk of neurological damage resulting from cord compression.[8–17] Cord damage may occur in these cases even with mild odontoid hypoplasia because the lax transverse ligament overrides the odontoid peg and is held back only by the apical and alar ligaments connecting odontoid and occiput. Perhaps even more importantly, when an os odontoideum is present, the detached upper part of the odontoid can move forward and sometimes remain permanently dislocated.[11] Pueschel *et al* feel that an atlantoaxial gap of 7 mm is sufficient to cause cord compression.[27]

Symptoms resulting from abnormalities of the atlantoaxial region in Down's syndrome appear to be rare Out of 161 people in our series, seven children and two adults had atlantoaxial instability, but none had symptoms. Semine *et al* found 10 children with atlantoaxial instability, only one of whom had symptoms.[6] Pueschel *et al* found seven out of 40 children with atlantoaxial instability had symptoms (18%), indicating an overall prevalence of symptoms in 2% of Down's syndrome children.[27] From a review of the world literature, together with personal reports, Pueschel *et al* collected 42 cases of symptomatic atlantoaxial instability. Two of these became symptomatic in their mid forties and the rest were much younger, with mean age incidence of 10·5 years. Children would be expected to suffer more symptoms because of the higher incidence of atlantoaxial instability and because the spinal cord is more easily compressed, being enclosed in a relatively smaller spinal canal. It is possible that the under developed odontoid peg in childhood also predisposes to overriding of the transverse ligament in the way described. Pueschel *et al* also noted that females have a greater incidence of symptoms of atlantoaxial instability by a factor of 2·3·1.[27] We cannot account for this, as our study showed no significant differences between the sexes in terms of the incidence of atlantoaxial instability, odontoid hypoplasia, or accessory ossicles.

There is understandable concern that flexion of the neck during certain sporting activities may damage the spinal cord in people with atlantoaxial instability. This has led to recommendations that people with Down's syndrome should have radiographs taken of the neck before participating in such sports as diving, trampolining, pentathlon events, and violent contact sports such as boxing.[1 2] Radiographs should also be taken before intubation for anaesthesia as excessive manipulation of the neck may be involved and this has resulted in cord damage in some people with atlantoaxial instability.[28] Most symptoms from atlantoaxial instability do not result from specific injuries and the DHSS has also recommended clinical surveillance to check on the development of signs or symptoms of cord compression in all people with Down's syndrome.[2] Surgery is indicated for those with cord damage, usually concerning posterior fusion of the atlas and axis vertebrae.[3]

While existing recommendations are sufficient for adults, there remains some difficulties in managing atlantoaxial instability in children. Some feel that radiographic screening should take place for all children with Down's syndrome as the school curriculum contains many activities that could damage the neck, for example, forward rolls in gymnastics and general rough and tumble activities. In the absence of radiographic screening, we know of some school authorities that restrict the activities of all children with Down's syndrome to prevent injuries occurring. Radiographic screening for atlantoaxial instability in children attending school, in addition to regular clinical checks, has therefore become a contentious issue. Those in favour of screening point to the importance of prevention of cord damage before it occurs,[29 30] especially when these individuals may not be able to indicate their symptoms and surgery is not always successful.[9] Those against radiographic screening point to the rarity of neurological damage from atlantoaxial instability. They feel this does not justify the use of an insensitive screening test which may cause undue parental anxiety and lead to the unnecessary restriction of activity in some people

Following our study, our current practice in Southern Derbyshire is to screen all children with Down's syndrome for atlantoaxial instability with radiographs of the cervical spine in the flexion and neutral position, at school entry around the age of 5. About 83% of the children are unaffected and allowed normal activity. The remaining 17% with atlantoaxial instability are restricted from diving, trampolining, gymnastics including forward rolls, and contact sport such as rugby and boxing. They are encouraged to take part in other sports such as running, swimming, and slow horse riding; radiographs are repeated yearly. All children are checked clinically for signs of cord compression on an annual basis. We plan to repeat the radiography on all children at the age of 10. Particular care is taken over those with both atlantoaxial instability and odontoid hypoplasia or accessory ossicles or with atlantoaxial instability alone exceeding 7 mm (1–2% of the total). We feel this is a reasonable approach to preventing serious neurological damage occurring in these children. Adults should be checked clinically on an annual basis and screened radiologically before taking part in certain sports or before anaesthesia. We will be evaluating this programme over the coming years, in particular to determine why some people with atlantoaxial instability go on to develop symptoms and whether restricting activity does in fact help prevent them.

We are grateful to the staff of the radiology departments of the Derbyshire Children's Hospital and Derbyshire Royal Infirmary and to physiotherapists working in community handicap teams who arranged *x* ray screening for adults with Down's syndrome. We are grateful to Dr C Murray-Leslie and Dr AP Abdulla for allowing us to study adult patients under their care Thanks also to Mrs Karen Purnell for typing the manuscript

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Short reports

Heaf test results after neonatal BCG

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SUMMARY Heaf testing was carried out on 98 preschool Asian children who had received a BCG vaccination. A strongly positive Heaf reaction (grade 3) occurred in only two children. Heaf testing can still be used in tuberculosis screening after neonatal BCG.

Most Asian children born in Britain have BCG vaccination in the neonatal period. A number subsequently present after contact with a case of tuberculosis. The interpretation of a positive tuberculin test in such children is difficult.

In an attempt to address this problem we have surveyed tuberculin positivity in previously vaccinated preschool British born Asian children.

Patients and methods

Asian children born in Derby have routine BCG vaccination given by specially trained health visitors using Dermo-jet (dose 0·1 ml). A routine check on conversion is made at three months by Heaf testing and infants with no response are revaccinated (about 2%).[1] From the population vaccinated in the standardised manner 98 preschool children were entered into the study. This represents about 5% of the Asian preschool population of Derby. They were recruited from one child health clinic when they or a sibling were attending for routine developmental surveillance or immunisation. Children were excluded from the study if they were currently taking oral corticosteroids or if they had had measles illness or immunisation in the preceding two weeks. None was thought to be at risk from tuberculosis before entering the study.

All children had a standard Heaf test with a spring loaded multiple puncture Mark 6 Heaf gun set at 1 mm for those less than 2 years old and 2 mm for those over 2 years, administered by one operator (PAGC). Results were read three to seven days later by the same operator. Children found to be grade 3 or 4 positive were referred to the local chest clinic for chest radiography and further review.

Results

Forty seven boys and 51 girls entered the study. All had a visible BCG scar. Fifty one children were of Pakistani Muslim origin; 35 were Punjabi Sikhs; seven Punjabi Hindus, and five were from other Asian ethnic groups. Eighty six of the children were first generation United Kingdom citizens. Overall there were 14 children (14%) who showed a grade 0 response, 75 (76%) with grade 1, seven (7%) with grade 2, two (2%) with grade 3, and none with grade 4. There was no significant difference in the responses at different ages (table).

Nineteen children had a family history of tuberculosis (four grade 0, 14 grade 1, one grade 2) and eight were known to have been in contact with someone who had been treated for tuberculosis (two grade 0, six grade 1). The two children with grade 3 responses were siblings of Pakistani Muslim origin; there was no family history of tuberculosis, no history of contact, nor of travel abroad. They were seen at the chest clinic, found to have normal chest radiography and no further action was taken.

Discussion

British born Asian children are at a much higher risk

Table *Number of children in each age group with each Heaf grade result*

Age (months)	*Heaf grade result*				
	0	*1*	*2*	*3*	*4*
6–18	4	30	1		
>18–30	4	12	1	1	
>30–42	3	18	1	1	
>42–60	3	15	4		
Total	14	75	7	2	

of tuberculosis than their white neighbours,[2] and for this reason most have BCG given in infancy. Figures on the degree of tuberculin positivity in early childhood after BCG vaccination in infancy have been reported from around the world but Capewell and Leitch make the point that positive tuberculin tests should be viewed in the context of the tuberculin profile of the local population.[3] A strongly positive Heaf test (grade 3 or 4) occurred in only 2% of our sample population.

An ethnically similar population to that reported here was studied in Birmingham by Grindulis.[4] The tuberculin positivity was assessed at 22 months of age and 50% of the children had a negative response to Mantoux 10 tuberculin units and 25% were found to have no BCG scar. In contrast all our children had visible scars and only 14% were entirely Heaf negative. This may reflect the effectiveness of a standardised vaccination procedure.[1] Strongly positive tuberculin reactions were rare in both studies (H Grindulis, personal communication). It should be pointed out, however, that the jet injection technique used in Derby is no longer recommended for BCG.

The increased risk to Asian children in Britain may be related to the ease of travel abroad and to relatives visiting. Many Asian children are seen at contact clinics and Ormerod has recently shown the effectiveness of a programme of chemoprophylaxis in this group.[5] The British Thoracic Society recommendations do not give clear guidelines on the management of the Asian child contact with previous BCG.[6] The results of this study suggest that the British born Asian child should be treated like his white counterpart.[6] When seen as a tuberculosis contact a strongly positive Heaf test should be taken as suggestive of recent infection, whether or not the child has previously had BCG. Such children should be carefully reviewed and considered for chemoprophylaxis or prolonged follow up.

We should like to thank the staff of the Derby Chest clinic for their help We are most grateful to Ranjit Bains, Harmesh Ark, and Jaspal Dosanjh for their help with interpreting.

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Tuberculin response after neonatal BCG vaccination

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SUMMARY Of a total of 846 children of Indian subcontinent ethnic origin given neonatal BCG vaccination, 823 (97%) were tuberculin positive when tested six to nine weeks after vaccination. The results show an initial immunological response to the vaccination. The possible reasons for the disparity between these results and others are discussed.

BCG vaccination shortly after birth in children of Afro-Asian ethnic origin is recommended by the Joint Tuberculosis Committee.[1] It has been routine policy to offer neonatal BCG to children of Indian subcontinent ethnic origin in Blackburn since 1963. After the report of Grindulis *et al* that showed a poor immunological response at 22 months after such vaccination,[2] a prospective study of early response to BCG vaccination was undertaken.

Subjects and methods

A total of 863 neonates of Indian subcontinent ethnic origin received BCG vaccination by intradermal injection from the resident paediatric medical staff between August 1984 and July 1985 inclusive. Home visits were carried out by community nursing staff and a tuberculin test carried out and read

72 hours later. Initially we planned to perform the tuberculin test at eight weeks after vaccination, but due to various reasons—for example change of address, visits to relatives hospitalisation, and intercurrent illness—in practice this was carried out from six to nine weeks after vaccination.

Of the 863 vaccinated children, 846 had a tuberculin test performed. Parents of two children refused permission, 15 had moved and could not be traced by nine weeks after vaccination. The tuberculin test used was the Tine test (Lederle). The reaction was graded 0–4, as with the Heaf test, reaction 0 being negative, grades 1–4 being positive. The presence of local BCG abscesses was also recorded

Results

The results are shown in the table. Twenty four children had small subcutaneous abscesses, with peak numbers found in those vaccinated in August (n=6) and February (n=5) at times of medical staff changeover. Twenty abscesses settled with dry dressings or aspiration, or both; four children were given short courses of topical or oral isoniazid.

Discussion

The results of this prospective study of a cohort of neonatally vaccinated children over one year shows that as judged by a positive tuberculin test, they have developed an immunological response by age 9 weeks. Two recent reports of response to vaccination neonatally or at 3 months also showed a very high positive tuberculin reaction rate. Hadfield and Allen prospectively showed a 98·3% positive Heaf test result three months after neonatal subcutaneous BCG given by Dermojet injector in Derby.[3] Packe and Innes, in a case-control study, showed a 94% positive tuberculin positive rate assessed three months after vaccination at age 3 months.[4]

The results reported by Grindulis *et al* are at variance with the results reported here,[2] and those from Derby and Birmingham, when tuberculin status was assessed two to three months after vaccination. A large number of factors determine whether tuberculin sensitivity develops after BCG vaccination, its initial strength, and the persistence of such tuberculin sensitivity.[5]

There are two possible explanations for the discrepancy between Grindulis's children and those reported here and elsewhere.[3] [4] (1) Grindulis's children did not have a high percentage of initial tuberculin positivity after vaccination. This could have been due to faulty vaccination technique, but this is unknown because no initial tests were carried out. (2) Although tuberculin sensitivity seems stable in older white children after BCG vaccination,[6] this sensitivity may not be stable in children from the Indian subcontinent ethnic group who have a different risk of tuberculosis in the United Kingdom.

It is likely that routine BCG vaccination at age 13 will be phased out by 1990 in England and Wales, and the only protection given to children of Afro-Asian ethnic origin will be that given to them by neonatal BCG. In view of the discrepancy between the early results of tuberculin testing in this ethnic group after BCG, and that reported two years after vaccination,[2] it is important to know the result of serial tuberculin tests in the Indian subcontinent ethnic group to see if there is a difference from the white ethnic group. We intend to carry out a further prospective study of a random proportion of the children reported in this paper, to assess their tuberculin response, four years after vaccination.

Table *Results from neonates vaccinated*

Age (weeks)	*Total No tested*	*No tuberculin positive**	*No (%) tuberculin negative*
6	239	235	4 (1·7)
7	183	181	2 (1 1)
8	309	295	14 (4·7)
9	115	112	3 (2·7)
Total	846	823	23 (2 7)

*All positive tuberculin reactions were grade 1 or 2
Analysis by χ^2 showed the only difference between the age groups was that infants aged 8 weeks had significantly more tuberculin negatives than those aged 9 weeks (χ^2 4·31, 0·05>p>0 01).

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Somatostatin analogue in short term management of hyperinsulinism

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SUMMARY Five infants with hypoglycaemia due to hyperinsulinism were treated for between three and 11 days with a somatostatin analogue, which raised the mean blood glucose concentration and lowered the glucose requirements in all. Somatostatin analogue appears to be useful in the short term management of these patients.

The prompt and effective treatment of hypoglycaemia due to hyperinsulinism reduces substantially the risk of long term neurological sequelae.[1] Glucose alone, even in high concentrations, may often fail to maintain blood glucose concentrations within the normal range and other measures are required to reduce the excessive concentrations of insulin [1]

Diazoxide has been used but this drug has major side effects and may be ineffective, especially in younger patients. Natural sequence somatostatin reduces insulin concentrations but its therapeutic use is limited by its half life of only two to three minutes so that it is necessary to administer it by continuous intravenous infusion.[2]

We have used long acting somatostatin analogue (SMS 201–995, Sandoz), which is more potent and specific than the natural peptide and can be given by subcutaneous injection, to treat five patients with hypoglycaemia due to hyperinsulinism.

Patients and methods

All patients were girls: four presented within a few hours of birth; the fifth presented at 9 months of age but gave a history from birth of hypoglycaemic symptoms, which had responded to two hourly feeds both day and night. Birth weights were above the 50th centile for gestational age (table).

Spontaneous hypoglycaemia with inappropriately raised concentrations of insulin and without ketonuria was confirmed in all patients. Four proceeded to laparotomy with subtotal (95–98%) pancreatectomy; histological features of nesidioblastosis were seen in three specimens and the fourth had those of insulinoma. The fifth patient, whose blood glucose concentrations were easier to control than those of the other patients, recovered normal blood glucose concentrations over a period of several weeks.

Blood glucose concentrations were measured hourly using the YSI Model 23A Glucose Analyser (Yellow Spring Instruments) Plasma insulin concentrations were estimated by a two antibody immunoassay.[3]

Results

A test dose of somatostatin analogue (1·0 μg) was administered subcutaneously to patient 1. Within minutes there was a rapid rise in blood glucose concentration and a concomitant reduction in glucose requirements, with the effect waning after four to five hours.[4]

Somatostatin analogue was then administered subcutaneously in three to four doses per day, commencing at 1·0 μg/kg/dose, but subsequently titrating the dosage against response, for a total of three to 11 days. Increasing doses of analogue led to a fall in glucose requirements (although never into the normal range for infants of 4–6 mg/kg/minute) and to a reduction of glucose oscillation. All patients continued to require intravenous treatment.

The figure (a) shows that in all patients the mean 24 hour blood glucose concentration rose after the administration of somatostatin analogue (4–9 μg/kg/day). The change in mean 24 hour blood glucose concentrations was significant (Wilcoxon's paired test; $p<0\cdot05$), although the change in glucose oscillation was not. Glucose requirements fell significantly ($p<0\cdot05$) (figure (b)).

Table *Details of patients*

Patient No	*Age at presentation*	*Birth weight (g)*	*Gestation (weeks)*	*Glucose (mmol/l)*	*Insulin (mU/l)*	*Diagnosis*
1	Birth	2610	36	0 4	24 1	Nesidioblastosis
2	Birth	4380	36	1 1	29 0	Nesidioblastosis
3	9 months	4000	40	1 5	21·1	Nesidioblastosis
4	Birth	4460	39	0 5	72·0	Insulinoma
5	Birth	2970	36	0 8	26 2	'Transient' hyperinsulinism

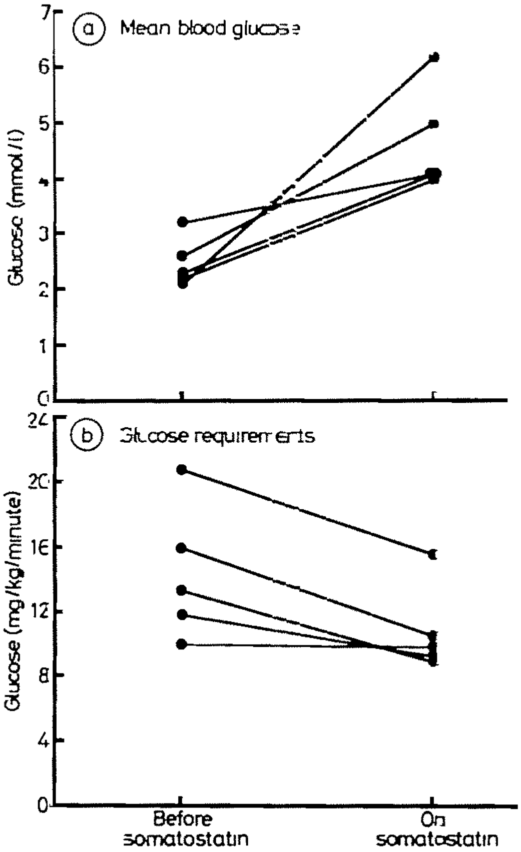

Figure *The effect of somatostatin analogue on (a) mean 24 hour blood glucose concentration and (b) 24 hour blood glucose requirements in the five patients*

Discussion

Somatostatin analogue was effective in the short term management of patients with hypoglycaemia due to hyperinsulinism. We use it to stabilise blood glucose concentrations and to enable lower concentrations of glucose to be used both preoperatively and perioperatively Given by regular subcutaneous injection its dosage regimen can be easily titrated against response and its short onset of action enables it to be of use in the emergency management of these patients, such as in the resiting of drips.

There are some theoretical reservations about the long term administration of somatostatin analogue to children as it has profound effects on many other hormones.[5] [6] Until the long term effects of somatostatin analogue are known, the treatment of choice in severe infantile hyperinsulinism should remain surgical, with maximal pancreatectomy. Premedication with somatostatin analogue greatly facilitates blood glucose control during the procedure.

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Recurrent pancreatoblastoma with inappropriate adrenocorticotrophic hormone secretion

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SUMMARY We describe a boy with recurrent pancreatoblastoma who developed Cushing's syndrome due to inappropriate adrenocorticotrophic hormone secretion.

Primary epithelial tumours of the pancreas are rare in childhood. Although islet cell tumours have previously been shown to produce inappropriate secretion of peptide hormones, we believe that this is the first report of a pancreatoblastoma producing adrenocorticotrophic hormone and an ectopic hormone syndrome.

Case report

A 22 month old boy presented with a firm, non-tender, asymptomatic abdominal mass of 12 cm diameter. He was normotensive with a blood pressure of 112/75 mm Hg, normokalaemic with a potassium concentration of 3·6 mmol/l, had an appreciably raised α fetoprotein concentration of 3670 μg/l (normal 2 μg/l), and a normal serum amylase of <300 IU/l (Phadebas method). An ultrasound scan showed a mass of mixed echogenicity crossing the midline and separate from the kidneys. Plain abdominal radiography showed the mass to be focally calcified

At operation the tumour was found to be arising from the pancreas, and a subtotal pancreatectomy was performed. Histological examination showed a malignant epithelial tumour with areas showing acinar differentiation, areas of poorly differentiated cells with frequent mitoses, and squamoid corpuscles. Immunoperoxidase methods showed strong staining for α_1 antitrypsin and α fetoprotein, but were negative for adrenocorticotrophic hormone, neurone specific enolase, and chromogranin. Electron microscopy confirmed acinar differentiation; no neurosecretory granules were seen. The appearance was of a pleomorphic pancreatoblastoma. Tumour was present at the line of resection indicating incomplete removal.

There was severe postoperative hypokalaemia (potassium concentration 2·1 mmol/l) despite intravenous supplements. The blood glucose remained stable Treatment was commenced with actinomycin D and vincristine in cycles of three weeks, and the serum α fetoprotein concentration fell to 18 μg/l. After three months the concentration of serum α fetoprotein rose; computed tomography and a radionucleide scan using labelled antibody to α fetoprotein showed a tumour deposit in the posterior mediastinum. The chemotherapy was therefore changed to cisplatin/etoposide, ifosfamide/etoposide, and doxorubicin in cycles of three weeks. The serum α fetoprotein then fell to normal concentrations, and treatment was continued for one year. He remained well off treatment for 18 months.

Three and a half years from first presentation he developed increasing fatigue, weight gain, and pigmentation. On examination he had a Cushingoid appearance, a palpable abdominal mass, and his blood pressure was 130/80 mm Hg. He was hypokalaemic (potassium concentration 2·5 mmol/l), and had a raised serum α fetoprotein concentration (590 μg/l). The plasma adrenocorticotrophic hormone concentration was 56 pmol/l (normal 2–18 pmol/l) and the urinary cortisol 2000 nmol/l (normal 55–740 nmol/l). A 24 hour serum cortisol profile showed loss of diurnal variation. Abdominal ultrasound examination confirmed the mass arising from the pancreatic remnant. Chest radiographs showed several metastases. A computed tomogram of brain showed no abnormality of the pituitary fossa and this together with the appreciably raised serum adrenocorticotrophic hormone, skin pigmentation, hypokalaemia, and lack of response to either dexamethasone or metyrapone, confirmed the diagnosis of inappropriate secretion of adrenocorticotrophic hormone. This was recurrent and metastatic pancreatoblastoma, as shown by the recurrent pancreatic mass seen on ultrasound examination and associated with a raised serum α fetoprotein concentration, although histological confirmation was not attempted.

Treatment was resumed with a combination of vinblastine, carboplatin, etoposide, and bleomycin. Unfortunately the tumour showed no response to two courses of chemotherapy, which was therefore withdrawn The child died three and a half years after diagnosis.

Discussion

Primary epithelial tumours of the pancreas are rare in childhood, and have a biphasic age distribution. Pancreatoblastoma like other blastomas of childhood affects children in the early years of life, has a slight male predominance,[1] and is sometimes associated with Beckwith-Wiedemann syndrome.[2] There have been two previous reports of pancreatoblastoma producing α fetoprotein.[3] Another tumour, unique to late childhood and early adult life, affects females almost exclusively, and has been given various names including ductuloacinar adenoma and papillary-cystic tumour of the pancreas. It usually follows a benign course.

Pancreatoblastoma can arise in any part of the pancreas and has distinct histological features including undifferentiated areas, acinar differentation, squamoid corpuscles, and the absence (by ordinary light microscopy) of islet cells. Originally thought to arise only from the ventral pancreas and therefore not to contain endocrine cells, it is now known that this tumour may arise in the distal (and therefore from dorsal) pancreas. The latter type seems to have a more insidious clinical onset, is non-encapsulated, and is associated with a worse prognosis.

There have been several reports of islet cell tumours producing hormones such as adrenocorticotrophic hormone, gastrin, glucagon, and growth hormone releasing hormone,[4] but non-islet cell pancreatic tumours are not associated with inappropriate secretion of peptide hormones. Insulin, gastrin, and somatatostatin have been shown by immunohistochemistry in pancreatoblastoma,[5 6] but we believe that this is the first case of pancreatoblastoma producing adrenocorticotrophic hormone and an ectopic hormone syndrome. Although tissue was not available from the recurrent tumour, it is likely that adrenocorticotrophic hormone secretion was the result of endocrine (islet cell) differentiation; this provides further evidence of the ability of this embryonic tumour to differentiate along both exocrine and endocrine lines.

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Intestinal disease in cystic fibrosis

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SUMMARY Three children with cystic fibrosis developed steatorrhoea unresponsive to changes in pancreatic supplements. The final diagnoses were chronic giardiasis, stagnant loop syndrome, and Crohn's disease. Refractory intestinal symptoms in cystic fibrosis merit further investigation.

It is still controversial whether the gastrointestinal manifestations of cystic fibrosis are primary or secondary,[1] although recent evidence shows that the basic defect in chloride transport is expressed in the intestinal epithelium.[2] Steatorrhoea, flatulence, abdominal pain, distal intestinal obstruction syndrome, and rectal prolapse are usually improved by adequate pancreatic supplementation, particularly with microsphere preparations.[1 3] Occasionally, however, high doses of these supplements, with or without H_2 antagonists, are ineffective. This can be caused by incorrect use of the supplements, or poor compliance, but coeliac disease and cows' milk protein intolerance have also been described in association with cystic fibrosis.[1] Investigating three children who presented in this way showed further treatable intestinal pathology.

Case reports

CASE 1

A 15 year old girl in early puberty complained of varying bowel habit over several months, passing up to five loose stools a day, often containing 'blobs of grease'. She also experienced rectal incontinence with laughter, and frequent abdominal pain after food. Her weight gain was poor, but this could not be explained by her chest disease. Stool microscopy showed fat globules but no parasites. At first poor compliance was suspected. A jejunal biopsy specimen, however, showed *Giardia lamblia* between the villi, and motile trophozoites were seen in the jejunal juice. After a three day course of high dose metronidazole she has been asymptomatic and her weight velocity has increased sharply.

CASE 2

A 7 year old boy had steatorrhoea, 8 g/day, despite a low fat diet (25 g/day) and up to 50 pancreatin microsphere capsules per day. His weight was between the 10th and 25th centiles, and height was on the 10th centile. Attempts to introduce a higher fat diet produced abdominal discomfort, distention, flatulence, and gross steatorrhoea. Cimetidine had no effect. As a neonate he had a Bishop Koop resection and ileostomy for meconium ileus, which was closed by clamping at 1 month. A year previously he had been admitted with subacute obstruction, which responsed to conservative management. Concentrations of serum iron, plasma ferritin, and vitamin A were low, and prothrombin time, vitamin D, and plasma bile acid concentrations were normal. Xylose absorption and a jejunal biopsy specimen were also normal, but fasting breath hydrogen was increased. Barium enema showed a persistent rounded filling defect near the caecal apex suggestive of a possible intussusception. A barium meal and follow through showed a dilated bowel loop running into a narrowed segment suggestive of a stagnant loop. At operation a stagnant loop was found and resected at the site of the previous operation. Over the next six months he tolerated a three fold increase in fat intake, with less than 10% steatorrhoea, and his weight increased to the 50th centile. He still has occasional abdominal pain and needs a high dose of supplements, but repeat breath hydrogen excretion and contrast studies are normal.

CASE 3

A 12 year old boy, treated for meconium ileus by a Bishop Koop ileostomy, presented with steatorrhoea. He complained of intermittent crampy abdominal pain, not always related to meals. He was otherwise asymptomatic, with weight and height following centiles between the 50th and 75th. Increasing his pancreatic supplement led to some reduction in his abdominal pain but shortly afterwards he was admitted with subacute obstruction, which resolved on conservative treatment. A jejunal biopsy specimen and breath hydrogen were normal on further investigation. Diatrizoic acid (Gastrografin) follow through showed a progressive distention in the distal ileum and a stricture in the ileocolic region. A barium enema showed free flow to the caecum, but no contrast entered the ileum. At operation an inflammatory mass affecting the caecum was found and a right hemicolectomy performed. The caecal wall was thickened and fibrous with a 1 cm constriction, and the findings on histology were those of Crohn's disease. His symptoms and steatorrhoea disappeared postoperatively but three months later recurred; barium studies showed an irregular stricture at the anastomosis, for which he is receiving prednisolone.

Discussion

We were surprised by the variety of intestinal pathology in these patients, who represent about 4% of our clinic. Many other patients have had symptoms of steatorrhoea that have responded to increased pancreatic supplements, and it was the failure of these three to do so that stimulated further investigation. In the latter two the extent of their problems was only fully realised after annual review.

Chronic giardiasis is a well recognised cause of steatorrhoea and failure to thrive in young children, but not in patients with cystic fibrosis. A recent survey, using stool antigen counter immunoelectrophoresis, found an increased prevalence of infestation in patients, but did not report clinical symptoms.[4] An adult patient with acute giardiasis has also been described who presented with vomiting, watery stools, weight loss, and hypoalbuminaemia.[4] Formation of a stagnant loop at the site of a previous Bishop Koop ileostomy is again well known,[5] but has not been described in patients with cystic fibrosis. There have been three case reports of Crohn's disease in association with cystic fibrosis: one in a child and two in adults.[6] Two presented with subacute obstruction, and all developed further typical complications. Many symptoms and signs, such as abdominal pain, diarrhoea, finger clubbing, and weight loss are common to both diseases, so diagnosis rests on imaging techniques and histology In our patient (case 3) diatrizoic acid (Gastrografin) was given for the dual purposes of treating subacute obstruction, which was believed to be due to the distal intestinal obstruction syndrome, and of imaging the bowel, as in neonates with meconium ileus.

Adequate management of gastrointestinal problems in cystic fibrosis improves the quality of life, and may, through better nutrition, improve their prognosis. The findings in our patients add to the list of gastrointestinal problems described in cystic fibrosis,[1] and show the importance of investigating steatorrhoea or abdominal pain, or both, that do not respond to manipulation of pancreatic supplements.

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Special advisory service for immunisation

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SUMMARY Among steps to improve immunisation rates in Clwyd an advisory service was introduced for children with immunisation problems. We report on setting up the service and the first two years of running it; during this time 191 children attended. Influencing parental and professional attitudes through education, counselling, and the demonstration of good practice is emphasised.

Ways to improve immunisation uptake have been considered in many districts. Initiatives in Clwyd, after a Welsh Office directive in 1985, aimed to increase uptake of pertussis (60%) and measles (57%) vaccines to at least 70% within 12 months: a short term goal towards World Health Organisation/ Department of Health and Social Security (DHSS) targets of 90% by 1990.[1]

Various measures introduced included a service based in the community for children with immunisation problems. Experience in setting up the service and the first two years of running the clinic is reported.

Methods

Aims were defined: to investigate and advise on immunisation in relation to specific medical problems; to ensure appropriate immunisation for those with genuine vaccine contraindications; to act as a focal point for education about immunisation; and to increase the proportion of children protected.

Referrals of any problems related to immunisation were accepted from doctors, preferably before or at the scheduled date for the procedure. Local paediatric approval was gained and general practitioners, child health doctors, and health visitors notified before monthly clinics commenced in October 1985. Sessions were conducted by a community physician with a designated health visitor, initially in clinic premises in Wrexham town centre, and from July 1986, in Rhyl.

Advice given strictly followed DHSS guidelines, and where possible, appropriate vaccine was administered immediately. Subsequent progress was monitored by health visitors. Detailed reports were sent to referring doctors, and action entered in the computerised immunisation schedule.

Results

From October 1985 to September 1987, 191 children attended. Community health doctors, who administer most immunisations in the district, referred 137 (72%), while 37 (19%) were from general practitioners, 15 (8%) from paediatricians, and two (1%) from other sources.

Ages ranged from 1 month to 16 years 2 months (mean 2 years 4 months, median 12 months). More boys (109) than girls (82) attended. Almost half (45%) were first born, with a third (31%) second in birth order.

Analysis of referrals showed 14 (7%) from social class I and II compared with 25% of all Clwyd children; 54 (28%) were from social class V as opposed to 14% of Clwyd children. Of the 173

Table 1 *Reasons for referrals*

Condition	*Frequency*		
	Personal history	*Family history*	*Total*
Convulsions	15	52	67
Vaccine reaction			
Local	10		
General	26	9	45
Atopy*	12	7	19
Allergy			
Drugs	2	—	2
Eggs	6	—	6
Developmental delay/ handicap	8	11	19
Perinatal/neonatal problems	14	—	14
Past recommended age for vaccine	12	—	12
Apnoea/breath holding after neonatal period	8	—	8
Severe parental anxiety	—	7	7
Cardiac lesion	3	—	3
Brain tumour	—	2	2
Death of sibling	—	2	2
Homoeopathic vaccine	2	—	2
Meningitis	1	—	1
Agammaglobulinaemia	—	1	1
Adoption	—	1	1
Cystic fibrosis	1	—	1
Total	120	92	212

*Includes asthma, eczema, rhinitis.

Table 2 *Vaccine of primary concern*

Primary concern	*Frequency*
Pertussis antigen (alone or as triple vaccine component)	77
Measles vaccine	54
Diphtheria/pertussis/tetanus vaccine	31
Diphtheria/tetanus vaccine	15
Polio vaccine	9
Tetanus antigen	5
Heaf testing/BCG vaccine	5
Rubella vaccine	2
All immunisation procedures	4
Total	202

families represented, 49 (28%) travelled between 10 and 30 miles to appointments

Table 1 shows reasons for referral and whether the child or a relative was affected. More than one reason was sometimes given. Table 2 indicates the vaccine primarily concerned: in 11 instances two procedures of equal concern are included. Ten requests were for pertussis immunisation of children aged 2 to 6 years. Two teenagers who had no previous immunisations were referred for consideration of all procedures.

Previous vaccine reactions were sufficiently severe for omission of pertusssis antigen in six instances and diphtheria antigen pending Schick testing in four. Measles vaccine with concurrent gammaglobulin was given in 11 cases, although antipyretic agents are now preferred. Pertussis vaccine was advised for three children over 2 years of age on specific medical grounds.

Apart from these, routine immunisation procedures were recommended and initiated in all instances, except for two families who rejected advice given. No reports of untoward reactions were received.

The target of 70% uptake was achieved in Clwyd within one year for measles vaccine (72%) but not for pertussis vaccine; after two years, levels of 77% and 71% respectively were reached.

Discussion

The service described has a dual role, with responsibility for individual children with immunisation problems, and with a broader remit to influence immunisation uptake in the community through education and demonstration of good practice. Education of professionals as well as parents is crucial to improving vaccine uptake; evidence suggests that DHSS guidelines are widely disregarded by health visitors and clinic nurses, who have an important role in determining parental attitudes.[2]

To achieve its purpose this type of service is ideally community based: hospital facilities are unnecessary, as proper interpretation of guidelines incurs risks no different to routine immunisation. The specialist nature of the clinics, however, provides reassurance, expertise for cases requiring special consideration, and practical training opportunities.

Siting of clinics and timing of appointments are important factors. Utilisation of services decreases with distance, and accessibility by public or private transport may have increased the willingness of families to travel to clinics.[3] Monthly sessions are necessary to accommodate some vaccine schedules. Potential immunisation problems should be identified before the first dose of triple vaccine whenever possible because of the association between pertussis and measles uptake and confusion about respective contraindications, a factor confirmed by the frequency with which parents enquired about both immunisations.[4]

The predominance of referrals from social class V was encouraging as immunisation uptake is known to have a social class gradient, although good levels can be achieved in situations of great deprivation.[5]

Presenting problems were similar to those reported elsewhere with genuine contraindications confirmed in few instances[6] Clinic interviews generated wide discussion and often advice was sought about children, vaccines, and schedules other than those primarily referred. First born children provided an opportunity to influence parental attitudes to immunisation of subsequent siblings. The extent to which advice was accepted indicates potential for improving uptake through careful parental counselling

Immunisation uptake rates in Clwyd have improved in concert with national trends to which various factors may have contributed. Theoretically the requirement for an immunisation advisory service of this kind should diminish if the educational component is successful. The effect of introducing the measles, mumps, rubella vaccine in October 1988 upon clinic referrals and vaccine uptake will be interesting.

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Platelet phenolsulphotransferase activity and 'abdominal migraine'

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SUMMARY Low platelet phenolsulphotransferase activity has been reported in adult patients with dietary sensitive migraine. Platelet activity of this enzyme was therefore measured in children having 'abdominal migraine' with probable dietary trigger and in controls. No significant difference was found in activity between the two groups. There was no significant correlation between platelet phenolsulphotransferase activity and age.

'Abdominal migraine' in children is characterised by recurrent central abdominal pain, and is typically associated with pallor and with gastrointestinal symptoms such as anorexia, nausea, or vomiting.[1] Despite the term being clearly self contradictory, as migraine comes from the Latin 'hemicrania' meaning '(pain in) the half of the head', it has become hallowed by usage, and reflects the suggestion that there is a relationship with common or classical migraine. Indeed, a positive family history of cranial migraine is often taken as a diagnostic criterion and, although not conclusive, evidence strongly suggests that there is a relationship between 'abdominal migraine' and common or classical migraine.[1] As there is, as yet, no diagnostic laboratory test for migraine, diagnosis is purely clinical, and it remains uncertain whether common pathophysiological mechanisms underlie the two conditions.

In many cases it is thought that attacks of 'abdominal migraine' can be provoked by articles of diet, with the list of foods implicated being very similar to those suggested as being linked to dietary cranial migraine. In particular citrus fruit, cheese, and chocolate are often cited as provoking agents.[2 3] Adult migraine patients who believe that dietary factors can provoke their attacks have significantly lower mean platelet phenolsulphotransferase P and phenolsulphotransferase M activity than patients with migraine not caused by diet or controls.[4 5] It therefore seemed of interest to measure platelet phenolsulphotransferase activities in a group of children suffering from 'abdominal migraine' with probable dietary trigger.

Patients and methods

Platelet suspensions in sucrose were prepared from blood collected from a group of patients attending Ealing Hospital as outpatients (n=21; 10 boys, 11 girls) and from a group of controls (n=13; six boys, seven girls). The major criteria used for making a diagnosis of 'abdominal migraine' were recurrent central abdominal pain (more than three attacks in not less than three months) accompanied by pallor, nausea or vomiting, or both, and a positive family history of migraine. At the time of study patients and controls were outside an attack and drug free. The mean (SD) age of patient group was 8·8 (2·5) years and of the control group 7·9 (3·2) years with a range from 3–13 years. Platelet samples were also collected from a group of adult controls (n=16) with a mean (SD) age of 36·6 (13·2) years with a range from 22 to 60 years.

Phenolsulphotransferase activity was assayed using phenol (final concentration 10 μmol/l) and tyramine (final concentration 130 μmol/l) as substrates for phenolsulphotransferase P and phenolsulphotransferase M respectively.[6] Platelet samples, prepared as described previously,[4] were used as enzyme source.

Results

No significant difference was found in either platelet

Table *Mean (SEM) platelet phenolsulphotransferase P and M activities in children with abdominal migraine and in controls*

	Specific activity (nmol/mg protein/10 min)	
	Phenolsulphotransferase P	*Phenolsulphotransferase M*
Patients (n=21)	0·037 (0·006)	0·382 (0·025)
Controls (n=13)	0·031 (0·007)	0·298 (0·043)

phenolsulphotransferase P or phenolsulphotransferase M activity between patients and controls (table). No significant correlation was found between platelet phenolsulphotransferase activity and age (r=0·09).

Discussion

The condition to which the clinical label of 'abdominal migraine' has been applied does have certain characteristic features in common with 'cranial' migraine in terms of family history, symptomatology, and triggering factors. The fundamental difference between the two conditions is in the location of the perceived pain and, as discussed earlier, this fact renders the label etymologically unsound. The justification for its continued use would be some firm physicochemical confirmation that a relationship does exist between 'abdominal migraine' in childhood and common or classical migraine in later life. The lack, to date, however, of any diagnostic laboratory test for migraine makes this confirmation difficult.

The finding that adult patients with migraine caused by diet have lower mean platelet phenolsulphotransferase activity than those with migraine not caused by diet or controls suggested the possibility that a similar biochemical deficiency might exist in children suffering from 'abdominal migraine' with probably dietary trigger. The results of this study, however, fail to show any such common biochemical deficiency. Even so, interpretation of these negative results must be made with caution because of the relatively small numbers of patients investigated. With this reservation, we would state that, at least, no further evidence has been educed pointing to a common aetiology of so called abdominal migraine and the more firmly established 'cranial' variety.

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Epidemiology of rheumatic heart disease

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SUMMARY We compared the incidence of rheumatic heart disease in elementary schoolchildren from low and high socioeconomic groups; children from one of the schools were rescreened 10 years later. The results showed that the incidence of rheumatic heart disease was significantly higher in low socioeconomic group but it is gradually declining.

Rheumatic carditis is one of the most important preventable heart diseases in children. Although in developed countries there is a dramatic decline in the incidence of rheumatic fever and rheumatic heart disease, they still remain a leading cause of heart disease in developing countries such as Turkey.[1 2] This difference is reported to be related to factors such as crowding, nutrition, hygiene, urban-rural residence, and access to medical care.[2–4]

This study was undertaken to assess the effect of socioeconomic state on the prevalence of rheumatic heart disease and whether there was any decline in the morbidity rate over the last decade with the improvement of medical facilities.

Method

The study consisted of two surveys. In the first part, in 1975, a total of 3039 children (1421 girls and 1618 boys) were screened. One group consisted of 1590 children from a shanty town who attended three primary schools, the other group consisted of 1449 children of a high socioeconomic group from a primary school in Ankara, Turkey. All the children were white.

Cardiac examination of each student was carried out by a paediatric cardiologist. For a diagnosis of rheumatic heart disease to be established a murmur was required to be of at least grade II/IV loudness, to have typical characteristics, and radiation. Children judged to have possible heart disease were further evaluated with electrocardiography, and chest radiography and echocardiography in some. Congenital cardiac diseases and innocent murmurs were excluded on these grounds.

The parents of the children filled in a questionnaire inquiring into the annual income, how many rooms their housing had, how many members their family consisted of, and whether or not the parents or a member of their families had had rheumatic fever or rheumatic heart disease.

In the second part of the study, in 1986, 538 children of the low income group from one of the primary schools previously studied were evaluated. The same procedures were undertaken.

The significance of the difference between parameters in different groups was analysed by Student's *t* test; p<0·01 was considered significant.

Results

In the first part of the study, in 1976, a total of 20 cases (nine girls, 11 boys) of rheumatic heart disease were identified, so that the total prevalence rate was 0·658%. Table 1 shows that the rate differed significantly between the groups. All of the children with rheumatic heart disease had mitral insufficiency, one with accompanying aortic valve insufficiency. Only three of them had mild exercise intolerance, one with dyspnea on effort. Four of these 20 children had a definite history of rheumatic fever.

On examining the questionnaires returned it was found that 75 out of 1317 (5·7%) of the children in the low socioeconomic group had a history of rheumatic fever; in the high socioeconomic group this was true in only 18 out of 815 (2·2%) children. Unfortunately some of these findings were not confirmed by medical records. Thus they may not be totally reliable.

In the low socioeconomic group, where the income levels were significantly lower than in the other group, the children were living in houses with about four people/room. In the high socioeconomic group all the children lived in houses with about one person for the comparable area.

Ten years later, when the pupils of one of the primary schools in the low socioeconomic group were screened, three (two girls and one boy) of the 538 children were diagnosed as having rheumatic heart disease; this gives a rate of 0·56%. One of the children also had rheumatic activation according to the Jones criteria. The previous rate in the same school was 0·94%. The difference between the two periods was significant (table 2).

Table 2 *The prevalences of rheumatic heart disease in a school in the low socioeconomic group 10 years apart*

	No of children	*No with rheumatic heart disease*	*Rate (%)*
1975	637	6	0·94
1985	538	3	0 56

The difference between the two groups was found to be significant (p<0·01).

Table 1 *Prevalence of rheumatic heart disease in the two groups*

	No of children	*No with rheumatic heart disease*			*Prevalence (%)*
		Girls	*Boys*	*Total*	
Low socioeconomic group	1590	7	10	17	1
High socioeconomic group	1449	2	1	3	0 2
Total	3039	9	11	20	0 6

The difference between the two groups was found to be significant (p<0·01)

Discussion

The prevalence of rheumatic heart disease among schoolchildren has previously been assessed in various countries.[3 5] In 1970 Morton *et al* found a relatively high prevalence of rheumatic heart disease among the schoolchildren in the San Luis Valley, which is a region of low socioeconomic level.[5]

Our higher rate for rheumatic heart disease in children from a low socioeconomic group is consistent with these reports.[4 5] The overall incidence, which was 0·6% in our series, is also considerably higher than in developed countries.

The second part of our study shows a decline in the morbidity rate of rheumatic heart disease in the last decade. As the children from only one school from the low socioeconomic group were screened we compared the result with the rate found in this school alone, in 1976. Although the number of children may seem inadequate a parallel decline noted in the number of patients with rheumatic heart disease seen in our cardiology clinics seems to support our thesis. The reasons for the decreasing incidence in rheumatic fever and rheumatic heart disease has not been completely understood. Markowitz agrees that widely disseminated programmes for the use of penicillin play an important part but insists that other unknown factors could be important.[3] Gordis has concluded that changes in the occurrence of rheumatic fever cannot be fully accounted for just by medical care and antibiotic use, but that we lack adequate information regarding other possible cofactors and that although group A streptococcus is the critical aetiologic agent of rheumatic fever, the disease is probably multifactorial in origin.[6] In Turkey we believe that improving medical care and greater access to health care have also appreciably influenced the documented decline. Further studies from developing countries might serve to enlighten the subject.

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Endemic bladder stones in Nepal

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SUMMARY Bladder stones account for a large proportion of surgical admissions in many developing countries. We report in detail the clinical features and risk factors of one such case, a 5 year old Nepali boy, and propose the theory that a low calcium intake, by causing hypocalciuria, predisposes to bladder stone formation.

Bladder stones are endemic in an area stretching as a belt from Turkey and Iran across India to Thailand and beyond to Indonesia and Papua New Guinea. However, they are rare in Africa.[1] They are also rare in the developed world, although this has not always been the case: they were common in England before the turn of the century when itinerant lithotomists flourished especially in 'stone districts', where the prevalence was unusually high, such as Norfolk.

In these areas of endemic bladder stones, boys are affected more than girls with a peak incidence at 5 years of age and the stones, which are rarely present in the kidneys, usually consist of uric acid, ammonium acid urate, or oxalate.[1] This is in contrast with the stones found in people from developed countries which are rare, occur in adults rather than children with a roughly equal sex distribution, are more common in the upper urinary tract, and usually consist of phosphates.

The following is, as far as we are aware, the first detailed case report and analysis of a bladder stone from Nepal. In addition to the commonly held dietary cause, we suggest that a low calcium intake may contribute to stone formation.

Case report

A 5 year old Nepali boy had a one year history of dysuria, and his urine was often cloudy and sometimes blood stained. He was one of five children living in a family in a hill village about five hours' walk from Pokhara, Nepal's second largest town. His father worked on the land. His diet was vegetarian, consisting mainly of white rice, sometimes eaten with lentils, vegetables in season, and milk less than once a week. He drank fresh spring water from a nearby source.

He weighed 13·5 kg (just below the third percentile for age). He was normal when examined awake, but under anaesthesia it was possible to palpate a hard plum sized suprapubic mass.

An abdominal radiograph showed a 4 cm radio-opaque bladder stone. The urine was sterile with a macroscopic sediment and a microscopic haematuria. Urine concentrations of calcium and oxalate were both low (0·42 mmol/l (normal 1·2–8·8) and 0·08 mmol/l (normal 0·2–0·5) respectively) and phosphate was normal (20·07 mmol/l (normal 11–32)). Serum concentrations of calcium (2·25 mmol/l), albumin (38 g/l), and urate (0·23 mmol/l) were normal while the concentration of phosphate was raised (3·24 mmol/l (normal 0·8–1·5)); creatinine was low (35 µmol/l (normal 50–130)).

A cystotomy was performed at which a beige 21 g stone was removed. He made an uneventful recovery, returning to his village one week later.

Both the stone and urine sediment were found to consist mainly of urates. X Ray crystallography showed a central core to the stone comprised mainly of ammonium acid urate with a much smaller proportion of calcium oxalate.

The mineral content of his drinking water was analysed. The concentration of calcium was low at 8·4 mg/l (Thames Water average at Surbiton, 99 mg/l). Other salts were as follows, with Thames Water average figures in brackets: magnesium 3·6 mg/l (4·3), phosphate 0·1 mg/l (3·1) and silicon dioxide 10·7 mg/l (range 3·8–11).

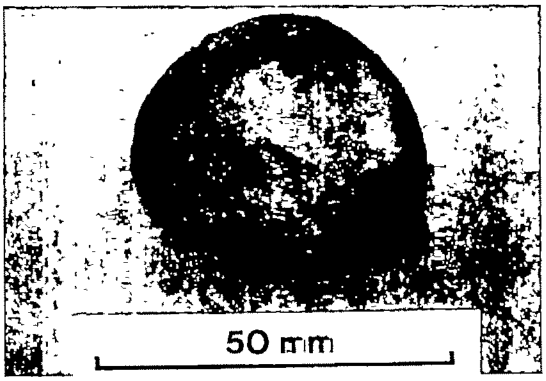

Figure *Bladder stone removed from Nepali boy.*

Discussion

Bladder stones are, in our experience, a common condition and an important cause of morbidity in Nepal. One of us (MA) anaesthetised about one such case each week at Gandaki Zonal Hospital, Pokhara: the stones were rapidly removed and placed among a large collection of similar stones, the heaviest of which were distributed to the surgical staff to be used as paperweights. Cystolithotomy constituted about 10% of operations on children in this hospital, a figure similar to that found in other hospitals in the 'bladder stone belt'.[1]

The cause of the uneven distribution of bladder stones is unknown. They are not causally related to dehydration, malnutrition, vitamin A deficiency, urinary tract infections, hypercalciuria, nor hyperoxaluria. The dietary theory has gained most acceptance and proposes that bladder stones occur in communities that subsist on just one cereal—for example, rice, millet, or wheat but not maize, the staple in much of Africa.[1] The probable mechanism for this association is that such a diet raises the urinary ammonia concentration which, in the presence of the high uric acid concentration found in all normal children (falling to adult concentrations by the age of 10 years), precipitates out as ammonium acid urate.[2] In this case it was not possible to measure the urinary ammonia concentration because of storage.

We hypothesise that a low calcium intake may also predispose to bladder stones by causing hypocalciuria, which has been shown in vitro to favour the precipitation of ammonium acid urate.[3] The calcium requirement of this boy was 400–500 mg a day[4]; this is much lower than in a temperate climate because of exposure to abundant sunshine. Nevertheless, his intake would have been inadequate: rice is a poor source of calcium, and milk was rarely taken. In hard water areas, drinking water can be a major source providing up to half of daily requirements but one litre of the drinking water in this case would have contributed a mere 8·4 mg of calcium. In response to a low calcium intake, hypocalciuria maintained the calcium balance in this case and he had not developed biochemical rickets. Other studies have reported that among stone sufferers there is a low dietary calcium intake, soft drinking water, and hypocalciuria; these studies, however, were performed before it was known that hypocalciuria could influence precipitation of ammonium acid urate and so a causal relationship was not suggested.[1 5]

The only other report linking drinking water to bladder stone formation is from Chad where stones were associated with high concentrations of silicon dioxide in the water[6]; the concentration was normal in the spring water drunk by the Nepali boy in this case.

Further study is needed to assess whether communities who eat a one cereal diet, as do most rural communities in Nepal, are protected from bladder stones if their dietary calcium intake is adequate or if the drinking water is hard.

We wish to thank the International Nepal Fellowship for arranging and allowing us the experience of medical work in Nepal We would also like to thank Dr K Joshi for allowing us to study his surgical patients, Dr A Symonds of Guy's Hospital, and Dr J Sutor of Birkbeck College for analysis of the stone We also thank Dr J Colbourne, Mr N Faber, and Mr J Green of Thames Water for analysis of the water specimens and Dr M Dillon of The Hospital for Sick Children, Great Ormond Street, and Dr G Haycock of Guy's Hospital for help in preparing this manuscript

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Neonatology—then and now (*CHM Walker*)

Neonatal sepsis (1961)

Two outbreaks of neonatal skin sepsis caused by *Staphylococcus aureus*, phage type 71

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One aspect of neonatal care which has not changed with the passage of time is the ever present threat of infection. The subject of this paper was a constant problem in nurseries at the time and paediatricians were learning of the ubiquitous nature of *Staphylococcus aureus* and *Candida albicans*. Staphylococcal pneumonia, meningitis, and osteomyelitis were not uncommon and the skin as an avenue of infection was always a worry.

In this paper 14 cases of major bullous lesions or abscesses caused by *S aureus* occurred in one hospital over a period of 15 days. *S aureus* was isolated also from one ward sister, a window ledge, and a partition. In the other hospital two cases occurred on the same day; a mother and a ward sister were found to be carriers and the ward was immediately closed. Efforts were directed towards the prevention and control of outbreaks of this kind and the management advice offered here was as follows:

> 'The organism isolated was found to be penicillin sensitive in all except one infant. Penicillin was therefore given to all except the most mildly affected. The skin lesions were treated with local applications of flavine or gentian violet in spirit. The latter seemed to be rather more effective. The carriers were treated with graneodin applied to the anterior nares, and excluded from duty until their nasal swabs were clear. When the second cases occurred, the practitioners attending infants discharged subsequently were asked to notify the hospital if any infection developed in either mothers or their infants. Only one such came to light, a single spot which rapidly disappeared. The wards concerned were closed to further admissions and the walls thoroughly cleaned, using 1:30 'savlon'. Following this, redecoration was undertaken.
>
> The blankets and mattresses used were stoved. Subsequently, cotton cellular blankets were introduced. The use of hand creams and soaps containing chlorhexidine was encouraged.
>
> It is our impression that, following these outbreaks, there is greater awareness of the possible dangers amongst the nursing staff, and there have been no further cases.'

Today. Where good general management and hygiene exists in the postnatal ward serious skin infections in the term baby have been reduced to a minimum and outbreaks such as those described in this paper are rare. But how things have changed in the special care baby units and intensive care units! Gone are the caps, masks, and overboots—and white coats or gowns seem to be a matter of personal choice. The nursery doors are open to all and sundry (almost) and checking staff for carrier state of organisms dangerous to the baby has been abandoned. This has made life very much easier for those working in and visiting these units, but it has also made it more difficult for everyone to remain vigilant and ensure scrupulous hand washing and exclusion of the obviously infected adult or sibling.

The type of organism may have changed but outbreaks of infection in these units still occur. Many are as, or even more, life threatening and difficult to eradicate than the old staphylococcus. The organisms are often less sensitive to available antibiotics and viruses lurk in the background waiting their chance to produce pneumonia and myocarditis. While attempts are being made to reduce some of these problems by reducing the duration of courses of antibiotics,[1] and while the value of routine immunoglobulin remains uncertain,[2 3] the battle between wily organisms and pharmaceutical scientists loses none of its intensity.

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Personal practice

Immunisation for all?

L POLNAY

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Success

Success of an immunisation programme depends upon enthusiasm, knowledge, and administrative efficiency. These are most important at the level of the individual practice or clinic. Immunisation figures for a district hide a huge range of local variation. Collection of local figures for a clinic or practice provides a powerful reinforcement of the practice and an excellent incentive to improve matters where outcomes are poor.

From the outset it must be clear who is responsible for immunising which children. Stating people's responsibilities in these terms is essential if immunisation uptakes are to be good. If it is not, the doctor or the community nurse would be content to wait for every immunisation initiative to be taken higher up in the hierarchy and merely respond to the demand that this generates. An example—general practitioners may immunise some children in their practice but not set out with the well thought out task of immunising them all.

Roles

Immunisations may be given by community nurses, general practitioners, or child health doctors. Doctors are an extremely expensive source of manpower for giving immunisations. Many district health authorities and general practitioners still rely upon doctors to carry out this activity. In community child health clinics in Nottingham immunisations are given by trained clinic nurses after a prescription has been written in the notes by the clinic doctor at the six week check.

In the world of 'do it yourself' blood pressure measurements I wonder how far off is the vending machine in which an appropriate limb is inserted and after putting in the token received by post the correct immunisation is given. Could we provide a 24 hour service?

Some professional problems and their solutions

Immunisation is a far more opportunistic process than we perhaps accept. The idea of the queue of prams and their occupants forming spontaneously outside every child health clinic when children are at the age of 3 months, 5 months, and 10 months, is but a community paediatrician's dream. In my own clinic in a deprived inner city area less than 10% of immunisations are given at scheduled times. Immunisation, therefore, represents a continuous campaign with them being given at all ages with modest peaks only around the target ages. Effectively, therefore, any clinic contact can be used for immunisation. Reminding the doctor or nurse about the immunisation status of the child by recording it boldly on the cover of the notes is an important means to identifying unimmunised children at any type of clinic attendance. Having found one such child at a clinic, the next step is to look at the immunisations of brothers and sisters who may be innocently accompanying them to the clinic or who should be asked to come next time. Records must of course be up to date if this method is to be useful.

The profession, nurses and doctors, have been shown to be uncertain in their knowledge about immunisation. Their drawers may be stuffed with outdated and confusing local and national memoranda on immunisation collected over the last 20 to 30 years. Spring cleaning of out of date memoranda and their replacement in Nottingham by our own 'Practical Guide to Immunisation' has provided doctors and nurses with practical and positive advice which is consistent across the district and enables them to answer the types of questions that parents ask, and to counsel parents effectively. The 'Practical Guide to Immunisation' is now included within a structured training procedure which includes a video and trainer's manual.[1]

Where in doubt doctors need a source of advice on immunisation; the availability by telephone of the community paediatrician enables nearly all uncertainties to be resolved very easily.

It is often difficult to judge contraindications from neonatal discharge letters. But those with direct care of the child at this time are probably those best able to judge whether or not genuine contraindications exist. It is therefore the practice in Nottingham to give positive advice in neonatal discharge summaries.

In the clinic

It is important to allocate an adequate amount of time for counselling parents. This is the only way to avoid children not being immunised because of 'asthmatic fits' or 'fits of temper' because sufficient time was not taken to get a proper history. Where parents are anxious or uncertain, rather than pushing them into a hasty decision, it is much better to arrange to see them again. Sometimes it is important to see other important people, for example, grandparents, whose views may be very important and who may be exerting considerable pressure on the mother. There is clearly an element of diminishing returns here in that there are some who will never be persuaded however often we may see them, but certainly a second and sometimes a third consultation followed up by opportunistic reminders can be very successful.

Appointment cards sent to parents need not be just bland invitations. They can carry an important health education message with regard to immunisation and can be personalised. Parent held records are also valuable in reinforcing the message.

In the clinic efficient administration is important to ensure that immunisation records can be quickly found and that these records are up to date. The clinic staff must also be aware of the need to update histories before immunisations are given.

Home visits can be valuable in mopping up pockets of unimmunised children. Very often the parent will attend clinic for subsequent immunisations after the demonstration to them of the importance that the doctor attaches to immunisation.

Inviting school children to the clinic to look at our work may provide an additional ally in the home. Parents may remark that after one of these activities their school aged children are consistently nagging them to bring the baby to the clinic for immunisation. Stickers or certificates for immunised children may prove to be additional incentives.

Summary

Immunisation programmes can be successful if there is continuous effort among those concerned, who have confidence in their knowledge, and a high level of commitment to immunisation. Training is required for all.[1] Feedback of results is essential.

Nottingham training package on immunisation (£90·00 each), training manual only (£5 50 each), and practical guide only (£2 00 each) can be obtained from Mrs K Tyler, Assistant Director Support Services, Community Unit, Memorial House, Standard Hill, Nottingham NG1 6FX

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Contemporary history

Dr Barbara Ansell
CBE, MD, FRCP, FRCS

On 30 August 1988 Dr Barbara Ansell retired from National Health Service practice after a distinguished career as a rheumatologist initially at the Canadian Red Cross Memorial Hospital, Taplow and then at the Clinical Research Centre, Northwick Park. There can be few paediatricians in the United Kingdom who have not had direct clinical contact with her over the past 30 years in her capacity as the doyenne of paediatric rheumatology. How then did she come to achieve this unique position?

She was born at home in Warwick in 1923 into a non-medical family and read medicine in Birmingham during the war years where she received a distinction in surgery. Her earliest paediatric influence came when she was a patient in Warwick County Hospital under the care of Wilfrid Gaisford, later to become Professor of Paediatrics in Manchester. House jobs in Birmingham were followed by her only formal paediatric training for two years in Northampton A further house job under Professor McMichael at the Hammersmith led to the MRCP diploma and a desire to pursue a career in cardiology. Attempts were made to dissuade her from this when told that there was a string of men waiting for posts in cardiology and that as a woman she would be well advised to think of something else (how times have changed?). A year in Chicago with Professor Robert Cark on an Eli Lilly scholarship is remembered as the most academically stimulating of her life and she returned full of enthusiasm. Still keen on pursuing a career in cardiology she was given a post as research fellow at the Canadian Red Cross Memorial Hospital at Taplow where Professor Eric Bywaters wanted her to study the heart disease of rheumatic fever. However, she very quickly became much more interested in the arthritic aspects of rheumatic fever and consequently all forms of arthritis in children.

In 1962 she was appointed consultant in a joint appointment between the NHS and the Medical Research Council a post she held until her retirement. One of her major research interests has been in the classification of arthritis in children and this formed the basis of a thesis for which she was awarded the degree of MD with distinction in 1965. Twenty years later most of the important findings of that work have been shown to be correct and a greater understanding of disease patterns and prognosis has emerged from her unique experience gained from long term follow up of patients over 20 to 30 years. She has pioneered novel management techniques with a specialised team of physiotherapists, occupational therapists, social workers, orthotists, and orthopaedic surgeons. Those who have worked closely with her have been deeply impressed by a phenomenal ability to remember details of children and their families, by the very practical nature of advice given, and by a gift for making instant friends with children

Honours have flowed her way. In 1978 she was elected a member of the British Paediatric Association and it was most appropriate that she gave the George Frederic Still Memorial lecture to the annual meeting of the BPA in 1981 on 'Chronic Childhood Arthritis Today'. A CBE in 1982 and an honorary FRCS in 1985 are among many other well deserved honours.

What then are Dr Ansell's main achievements? The Taplow group quite clearly showed that early active management of children with arthritis could lead to significant improvements in outcome. Children from all over the United Kingdom and many other parts of the world, benefited from the high quality inpatient management and supervision of subsequent treatment from her unit. However, it was clear that Taplow would have to close (it was built in 1915 with an estimated life of 10 years!) and Dr Ansell, who always believed that the future lay in good regional services, set about training and influencing paediatricians throughout the country. She inspired the setting up of regional clinics, usually staffed by a paediatrician and rheumatologist, and for the past 10 years she has spent much of her time visiting these centres on a regular basis, ensuring a smooth transition from the centralised care of former years. There are also many countries in the world where there are paediatricians who have been trained at Taplow and later Northwick Park, and who have subsequently returned to the unit to once again partake of her most generous professional and personal hospitality. When asked what her greatest contribution has been she replies 'training doctors all over the world that children with arthritis are not just miniature adults'. Interestingly she feels that her most influential publication, of which there are over 300, is her booklet for parents *When your child has arthritis*. Of hopes for the future, she would like to see more money and effort being devoted to basic research.

She was born on a Thursday and therefore had 'far to go'. Dr Ansell has not only come a long way but she has brought many others with her. Paediatricians and children with arthritis from all over the world are grateful to her and we wish her many happy years of retirement during which she intends to devote much of her energy to the charity 'Arthritis Care'.

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Annual statistical review

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This is the second in a series of annual reviews of national statistics relating to children. As this is a recent addition to the topics covered by *Archives of Disease in Childhood,* we again invite comments from readers on the suitability of the statistics covered and suggestions as to what additional material should be included.

Demography

The annual number of births in the United Kingdom has been rising since 1982 and 1986 continues this trend with 755 000 births, an increase of over 3000 since the previous year. Within this, the striking feature has been the rise in the number of illegitimate births while the number of legitimate births has fallen. In 1986, 21% of births in the United Kingdom were illegitimate.

Illegitimate births may be subdivided into those registered by one parent and those registered jointly by both parents. The numbers in both groups have risen though the latter shows the greater increase. These trends have obvious implications for infant and childhood mortality and morbidity rates. They are shown in table 1.

Mortality

INFANT MORTALITY

In 1986 there were almost 6000 infant deaths in England, 580 in Scotland, and 350 in Wales. Annual trends in infant mortality rates in Scotland and Wales need to be interpreted with care because random variation within the small number of deaths will produce swings in the mortality rate from year to year. This caveat is even more pertinent when infant mortality is broken down into its component neonatal and postneonatal mortality rates. Table 2 shows the annual trend in neonatal, postneonatal, and infant mortality rates in England, Scotland, and Wales from 1982 to 1986. The feature of this table that must be of some concern is the rise in infant mortality for England in 1986, which exceeds not only the rate for 1985 but also for 1984. This is entirely due to a rise in the postneonatal mortality from 3·91 to 4·24/1000 live births; neonatal mortality has shown an uninterrupted fall, although the rate of improvement has been slowing down.

The increase in the postneonatal mortality rate in 1986 occurred across all maternal age, parity, social class, and legitimacy/illegitimacy groups. The excess compared with 1985 was largely among male infants. Analysis of the data by quarters of the year show that postneonatal mortality was particularly high in the January-March quarter of 1986 and a suggested explanation was the severe spell of prolonged cold

Table 1 *Live birth registration (000s) 1980–6 in England and Wales*

Year	*Legitimate live births (%)*	*Illegitimate live births*		*All live births (%)*
		Jointly registered (%)	*Solely registered (%)*	
1980	578·9 (88·2)	44·2 (6·7)	33·2 (5·1)	656 2 (100)
1981	553·5 (87 2)	47·1 (7·4)	33·9 (5 3)	634 5 (100)
1982	536·1 (85·7)	53·4 (8·5)	36·5 (5 8)	625 9 (100)
1983	529·9 (84·2)	60·8 (9·7)	38 4 (6·1)	629·1 (100)
1984	526·3 (82·6)	69·9 (11 0)	40 6 (6·4)	636·8 (100)
1985	530·2 (80·8)	81·8 (12 5)	44 4 (6 8)	656·4 (100)
1986	519 7 (78·6)	93·5 (14 1)	47 8 (7·2)	661·0 (100)

Source OPCS Series FM1 No 15.

Table 2 *Trends in infant mortality 1982–6*

	1982	*1983*	*1984*	*1985*	*1986*
Neonatal mortality rate					
England	6·2	5·8	5·5	5 3	5·2
Scotland	7·1	5·8	6·4	5·5	5·2
Wales	6·9	6·7	5 7	5·8	5·6
Postneonatal mortality rate					
England	4 6	4 2	3·9	3·9	4 3
Scotland	4·3	4 1	3·9	3·9	3·6
Wales	3 7	4 0	3·1	4·0	3·9
Infant mortality rate					
England	10·8	10·0	9·4	9·2	9·5
Scotland	11·4	9·9	10·3	9·4	8·8
Wales	10 6	10·7	8·8	9·8	9·5

Source. OPCS Population Trends 50, Winter 1987.

weather that was experienced in that quarter. Data recently available for 1987 indicate that the infant mortality rate has fallen again to 9·2/1000.

Cause specific neonatal and postneonatal mortality rates for England and Wales 1985 are shown in table 3. For neonatal mortality all the major cause of death categories show a decrease compared with previous years. For postneonatal mortality no trend is obvious. This is consistent with the all causes rate being virtually the same in 1985 as it was in 1984. The cause specific rates for 1986 are not yet available.

International comparisons of postneonatal mortality are given in table 4 which is an extension and updating of a similar table given in the previous statistical review. It is apparent that, for most countries shown in the table, there has been a levelling out of the postneonatal mortality rate. Between countries the rates have stabilised at different levels but within countries there tends to be a fluctuation in the annual rate. The increase in postneonatal mortality in England must be viewed against this background.

Table 3 *Neonatal and postneonatal cause specific mortality rates in England and Wales 1985*

Diagnosis	*Rates/1000 live births*
Neonatal mortality	
Diseases of the respiratory system (ICD 460-519)	0·07
Congenital anomalies (ICD 740-759)	1·70
Certain conditions originating in the perinatal period (ICD 760-779)	3·21
All causes	5·32
Postneonatal mortality	
Infectious and parasitic diseases (ICD 000-134)	0·12
Diseases of the respiratory system (ICD 460-519)	0·58
Congenital anomalies (ICD 740-759)	0·67
Sudden death cause unknown (ICD 798)	1·67
All causes	3·86

ICD International Classification of Diseases Source OPCS Series DH3 No 19.

Table 4 *Postneonatal mortality in various countries (rates/1000 live births)*

	*Category**	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*
Australia	a	0·68	0·67	0·75	0·73	0·62	0·65	
	b	0·29	0·20	0·18	0·23	0·19	0·23	
	c	1·64	1·69	1·78	1·74	2·07	1·96	
	d	3·60	3·50	3·64	3·57	3·76	3·74	
England and Wales	a	0·83	0·90	0·93	0·86	0·82	0·73	0·74
	b	1·04	0·88	0·88	0·71	0·55	0·58	0·47
	c	1·45	1·57	1·76	1·69	1·65	1·71	1·97
	d	4·38	4·41	4·56	4·29	3·92	3·98	4·27
France	a	0·92	0·89	0·84	0·76	0·74	0·67	
	b	0·22	0·18	0·16	0·15	0·13	0·12	
	c	1·23	1·36	1·61	1·74	1·52	1·66	
	d	4·25	4·22	4·20	4·13	3·63	3·72	
West Germany	a	1·16	1·12	1·05	1·03	0·96	0·81	0·76
	b	0·47	0·32	0·25	0·28	0·24	0·21	0·17
	c	1·15	1·34	1·39	1·33	1·39	1·58	1·59
	d	4·76	4·64	4·59	4·39	4·15	3·99	3·76
Japan	a	0·95	0·91	0·87	0·81	0·82	0·76	0·77
	b	0·35	0·32	0·27	0·24	0·23	0·20	0·20
	c	0·10	0·11	0·12	0·13	0·14	0·13	0·16
	d	2·55	2·42	2·34	2·33	2·28	2·09	2·14
The Netherlands	a	0·80	0·76	0·83	0·78	0·87	0·89	
	b	0·19	0·21	0·19	0·11	0·16	0·27	
	c	1·00	0·99	1·06	1·32	1·34	1·13	
	d	2·93	2·86	3·16	3·10	3·25	3·05	
Scotland	a	0·99	0·79	0·82	0·72	0·68	0·53	
	b	0·48	0·48	0·38	0·30	0·40	0·18	0·15
	c	1·83	2·12	1·98	1·80	1·87	2·01	2·19
	d	4·32	4·41	4·24	4·10	3·98	3·90	3·62
United States	a	0·70	0·67	0·63	0·64	0·62		
	b	0·39	0·34	0·31	0·33	0·30		
	c	1·54	1·49	1·46	1·48	1·47		
	d	4·12	3·91	3·82	3·91	3·79		

*Category (ICD 9): a, congenital anomalies, b, diseases of the respiratory system, c, signs symptoms and ill defined conditions, and d, all causes. Source: WHO Annual Statistics, various years.

International differences in postneonatal mortality due to congenital malformations are small. Greater variation is seen in the rates for respiratory diseases and signs, symptoms, and ill defined conditions. This latter category is virtually a synonym for cot death. There are problems in interpreting these trends because, in recent years, there has been a diagnostic transfer from respiratory to cot deaths—that is, the summation of the two causal groups shows little change over time.

The analysis of mortality rates according to maternal age, parity, and social class from the routine data set linking infant death and birth registration documents for 1985 is shown in table 5. Comparison with 1984 shows an improvement in most of the rates relating to each variable recorded in the table. The vulnerability of women in the youngest age group—that is, less than 20 years—for perinatal, neonatal, and postneonatal mortality is evident. In the social class section of the table those classified as 'Others' include the unemployed, students, and members of the armed forces.

BIRTHWEIGHT SPECIFIC MORTALITY AND LOW BIRTH WEIGHT

Interest in birthweight specific mortality rates continues predominantly because of developments in neonatal intensive care. They are being used as outcome measures for determining the effectiveness of special and intensive care units.

One side effect of the development of intensive care facilities has been the rise in the proportion of births that are extremely low (<1000 g) or very low (1001–1500 g) birth weight. Time trends are shown in the figure. Almost certainly this is, at least in part, an artefact as these infants are now resuscitated and registered as live births whereas in the past they would have been classified as abortions, not registered, and not enumerated. The extent to which this occurs will obviously vary between districts depending on the provision of facilities for intensive care and clinical policy of the unit. Because extremely and very low birthweight infants are at high risk of dying, any proportionate increase in their numbers will have an adverse effect on the overall mortality rate. Ideally standardisation for birth weight should

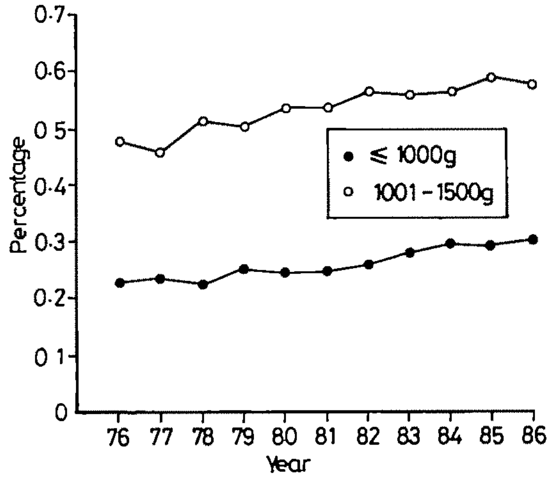

Figure *Proportions of live low weight births in England and Wales 1976–86.*

Table 5 *Perinatal, neonatal, and postneonatal mortality by maternal age, parity, and social class for England and Wales in 1985*

	Maternal age					*Parity*				*Social class*						
	<20	*20–24*	*25–29*	*30–34*	*35+*	*0*	*1*	*2*	*3+*	*I*	*II*	*III (non-manual)*	*III (manual)*	*IV*	*V*	*Others*
								Legitimate births								
Perinatal mortality*	12·5	9·1	8·2	9·7	11·6	10·2	7·7	8·8	12·6	7·7	7·5	8·8	9·2	11·1	12·4	11·7
Neonatal mortality†	8·3	5·2	4·5	4·8	6·2	5·4	4·5	4·8	6·3	4·7	4·2	4·6	4·9	6·1	6·3	7·1
Postneonatal mortality†	6·8	4·2	2·8	2·8	2·9	2·3	3·7	4·4	5·2	2·4	2·8	2·6	3·2	4·0	5·2	6·2
								Illegitimate births								
Perinatal mortality*	11·9	11·3	11·9	13·1	18·0											
Neonatal mortality†	6·4	6·2	6·6	6·4	7·5	Not applicable				Not applicable						
Postneonatal mortality†	7·1	6·5	4·7	4·0	3·9											

*Rate/1000 total (live and still) births; †rate/1000 live births.
Source OPCS Series DH3 No 18

be carried out when mortality comparisons are considered, for example, comparisons between districts or over time.

The 1985 and 1986 birthweight specific mortality rates for England and Wales are shown in table 6. There is no striking feature to report on from this table, there have been marginal decreases or increases in the birthweight specific mortality rates.

Birthweight specific perinatal mortality rates for Denmark, England and Wales, and Scotland are given in table 7. Difficulties occur in compiling such tables because, while rates may be provided, they are not for the same birthweight groups and the numerators and denominators are not published. Other important caveats relate to the very low birthweight and the weight not stated groups. The former is affected by whether or not a very low birthweight baby born dead is registered as a stillbirth or is not registered and therefore not counted because it is classified as an abortion. The infants for whom birth weight is not stated are biased towards very low birth weight and the proportion so classified will affect the comparison.

Morbidity

INFECTIOUS DISEASES

The National Congenital Rubella Surveillance Programme holds data on children classified as cases of confirmed or suspected congenital rubella. Since 1980 a range of ascertainment sources have provided the data and the number of cases of congenital rubella syndrome and congenital rubella infection are shown in table 8. Defects have not so far been recorded in any child after rubella has been proved serologically after the 17th week of pregnancy.[1] In contrast, when infection occurred before the seventh week of pregnancy, no child escaped damage.

In 1986, in Great Britain, immunisation of children within two years of birth for diphtheria, poliomyelitis, and tetanus remained unchanged from 1985 at 85%. For whooping cough and measles there were slight increases to 66% and 71% respectively.

HOSPITAL STATISTICS

The recognition of the psychological trauma associated with admission of children to hospital has led to decreasing lengths of stay and a trend for treatment as day cases. Associated with this trend is the attendance of ward attenders who are defined as patients attending a ward who do not require the use

Table 7 *International comparisons of birthweight specific perinatal mortality 1985*

Birth weight (g)	*Denmark*	*England and Wales*	*Scotland*
<1000	507 2	577 3	609·1
1000–1499	271 1	229·5	262 6
1500–1999	79 1	93·7	99·3
2000–2499	27 2	28·3	28·1
2500–2999	6·6	7·2	7·1
3000–3499	2 2	2·9	2 4
3500–3999	2 6	1 8	1·9
≥4000	1·9	3·1	2·9

Source. Medicinsk fødselsstatistik 1985; OPCS Series DH3 No 18, 1985, Scottish Stillbirth and Neonatal Death Report, 1987

Table 8 *Cases of congenital rubella syndrome/infection by year of birth*

	Year of birth							
	1980	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*
Defects	28	12	29	38	25	15	9	2
No defects	6	4	9	25	23	5	7	2
Total	34	16	38	63	48	20	16	4

Source· Communicable Disease Report, Weekly Edition 88/15

Table 6 *Birthweight specific mortality for England and Wales 1985 and 1986*

		Birth weight (g)							
		<1500	*1500–1999*	*2000–2499*	*2500–2999*	*3000–3499*	*3500–3999*	*≥4000*	*Not stated*
Stillbirth*	1985	154·5	63 8	18·7	4·8	1·9	1·0	2·0	64·7
	1986	153·3	53 3	18·8	4·4	1·8	1·2	1·7	42·9
Perinatal*	1985	350·1	93·7	28·3	7·2	2·9	1·8	3 1	195·0
	1986	345·5	85 0	27·3	6·6	3·0	2·0	2 7	187·1
Neonatal†	1985	260·4	37 8	12·3	3·4	1·6	1·2	1·5	156·7
	1986	262·3	40·1	10·7	3 0	1·6	1·2	1·3	163·5
Postneonatal†	1985	39·8	17 1	9·1	4 6	3·0	2·4	2·3	10·4
	1986	40·1	20 9	9·0	4·9	3·2	2·7	2·4	17·6
Infant†	1985	302·2	54·8	21·4	8 1	4·5	3·6	3·8	167·1
	1986	302·4	61 1	19·7	8·0	4·8	3·9	3·7	181·1

*Rate/1000 total births; †rate/1000 live births. Source OPCS Monitor DH3 87/1, 88/1

Table 9 *Percentage of general practitioner consultations for selected ICD chapter by age*

	Age (years)	
	0–4	*5–14*
Infectious and parasitic disease (ICD 001–139)	11 4	12 4
Diseases of the nervous system and sense organs (ICD 320–389)	15 8	14·1
Diseases of the respiratory system (ICD 460–519)	30·1	32·0

ICD: International Classification of Diseases
Source OPCS Series MB5 No 1

of a hospital bed. A survey carried out by the National Association for the Welfare of Children in Hospital found that in the two weeks of the study, ward attenders formed 24% of all patients in the 33 wards for which data were available. Of the ward attenders 34% were for post discharge reviews and 23% for planned procedures.[2]

GENERAL PRACTICE

The third national study presented morbidity statistics from general practice 1981–2. It showed that 98% of children under 5 and 66% aged 5–14 consulted their general practitioner in the study year. The major reasons for consulting a general practioner are shown in table 9.

Social habits

Trends in the smoking and drinking habits of children have obvious important implications for their subsequent health.

SMOKING

A survey carried out by the Social Survey Division of the Office of Population Censuses and Surveys (OPCS) found that between 1984 and 1986 there was a pronounced fall in the proportion of boys who smoked cigarettes regularly (that is at least one cigarette a week) in England and Wales from 13% to 7% and in Scotland from 16% to 10%.[3] Among girls in Wales and Scotland there was a clear though less pronounced fall in the prevalence of smoking but in England there was no significant change. Smoking among secondary school children in Scotland, England and Wales is more prevalent among girls (12%) than in boys (7%).

ALCOHOL

The OPCS adolescent drinking survey found that among 13 year olds, 29% of boys and 11% of girls drank at least weekly, while at 15, 52% of boys and 37% of girls were drinking weekly.[3] The youngest adolescents drink mostly at home or at the homes of relatives or friends. As they grow older they continue to drink at home but also begin to drink in clubs and discos.

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Archives of Disease in Childhood 1988, **63,** 1516–1517

Referees and staff 1987–88

Our referees

Submitted manuscripts are initially seen by the Editors who then send them to one or two expert referees for assessment. We thank the following people who kindly reviewed papers for our Journal in 1987 and 1988. Their expertise and the time so generously given has been a major factor in maintaining high standards.

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Staff changes

We thank Janine Oesi, who is on maternity leave, for her efforts for the Journal over the past year. We welcome Jacinta Marshall as our new Editorial Assistant.

Archives of Disease in Childhood, 1988, **63,** 1518–1520

Correspondence

Immediate effects of albumin infusion in ill premature neonates

Sir,

The paper on albumin infusion in neonates by Greenough *et al* gives us several reasons for concern [1] One issue, the lack of non-treated comparison infants, has been dealt with in the commentary [2] The weight loss in most preterm infants is, in our experience, independent of their degree of oedema and plasma albumin concentration, even in those sick with respiratory distress syndrome We cannot agree, therefore, that it has been shown that albumin infusion caused the observed diuresis.

The authors have apparently measured urine passed in a number of discrete micturitions during a predetermined time interval, and have called this urine output Bladder emptying is highly irregular, however, and variably incomplete in all sick preterm infants. We have observed micturition patterns in very low birthweight infants and have found the intermicturition interval to vary from less than one hour to more than 12 hours, and the volume passed from a few drops to 20 ml/kg. Measurement of urine passed in an interval of six hours is therefore an inaccurate estimate of renal water excretion rate, especially when this is at a maximum of about 10 ml/kg/6 hours as stated, and most certainly when only 0·7 or 1·3 ml is passed. In addition, parametric statistics have been used to compare these estimates of water excretion rates, which are highly unlikely to be normally distributed

We are given urine output uncorrected for body size (water excretion rates in ml/kg/day would have been more helpful). Nevertheless prealbumin urine flow rates are low in all the infants studied (mean perhaps about 30 ml/kg/day). This is probably because water input in these infants was low; although this was not specified, it is implied that it remained around 40 ml/kg/day in the first few days. We give much larger volumes and only in exceptional cases is there an inability to excrete administered water, as has been found elsewhere in well babies.[3] We dispute therefore the contention that the prolonged oedema and oliguria are necessarily due to failure of renal water homoeostatic mechanisms.

The study was designed to show whether albumin is effective in 'treating' hypoalbuminaemia. We find it hardly surprising that the rapid infusion of 20% albumin (200 g/l) into a vascular space where the albumin is mean 27 g/l raises the albumin concentration. The addition of 1 g/kg of albumin into what is probably a vascular space of about 50 ml/kg, however, raises the albumin concentration by only [illegible] g/l. This implies that an appreciable volume expansion has occurred, perhaps by as much as 50% if there really is no extravascular leak of the albumin. Such a volume expansion is likely to have caused an acute increase in glomerular filtration rate, which would have flooded the immature renal tubules with an increased filtered load, when reabsorptive capacity is already compromised. This will have resulted not only in the observed diuresis, but also in an acute loss of other solutes, especially sodium, where renal sodium conservation is already poor.

In summary, the authors do not give any evidence that a rapid albumin infusion does cause a diuresis, let alone that the resulting acute disturbance in vascular and renal physiology is beneficial. We believe that such a disturbance is more likely to be harmful and that, in the absence of convincing scientific support, this practice should not be promoted

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Dr Greenough comments.

We thank Dr Wilkins *et al* for their interest in our short report on albumin infusion in the neonate.[1] We have, however, already provided data within the report to answer their concerns. In summary: Dr Wilkins *et al* claim that, in their experience, weight loss and diuresis are independent of the degree of oedema and plasma albumin concentration, but unfortunately they do not present their data. In our study to document the effect of albumin infusion we measured both urine output and change in weight. Comparison of the control and treatment periods, during which no other changes were made, showed in eight of 10 infants urine output increased and all 10 infants lost weight after the infusion As this response was seen in infants in varying stages of their respiratory illness the increase in urine output is likely to be associated with the albumin infusion.

We agree that the measurement of urine output in the preterm neonate is difficult We therefore used the same method of urine collection during both periods, and in addition measured weight change. In the absence of change in fluid input and phototherapy status, changes in weight reflect changes in urine output. Using non-parametric statistics confirmed that both the increase in urine output ($p<0{\cdot}05$) and decrease in weight ($p<0{\cdot}01$) after the infusion were significant.

Albumin was not given rapidly, but as part of the daily fluid requirements and at the same rate. This method of infusion seems unlikely to cause an appreciable volume expansion with an acute increase in glomerular filtration rate and loss of solutes This hypothesis is supported by the lack of change in urea and electrolytes after the albumin infusion (results section). Albumin concentrations were only measured daily (methods section), the post infusion concentration thus reflects the amount remaining in the vascular space at that time, in infants in whom protein leaks are well recognised.[2]

The aim of our preliminary study was to investigate, using infants as their own controls, if albumin infusion was effective in treating hypoalbuminaemia in normotensive sick infants.[1] We were able to show that albumin infusions were effective and associated with a significant increase in urine output. Using these data we have now designed a randomised controlled trial to investigate the duration of effect of albumin infusions and if this treatment alters clinical status.

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Cystinosis and vitamin D

Sir,

Katzir *et al* reported a case of nephrogenic diabetes insipidus, cystinosis, and an abnormality of vitamin D metabolism.[1] The idea that nephrogenic diabetes insipidus might herald cystinosis is interesting Their analysis of the serum vitamin D metabolite concentrations on the patient, however, should not be regarded as a feature of the described association but rather part of the natural course of cystinosis In 1983 Steinherz *et al* reported on the circulating vitamin D metabolites in nephropathic cystinosis [2] In this study, 10 cystinotic patients with various degrees of functional renal impairment were screened for their vitamin D metabolites. The mean (SD) concentrations of 24,25 dihydroxyvitamin D_3 ($24,25(OH)_2D_3$) were reduced in those patients treated with low dose of ergocalciferol (<25 µg) but within the normal range in the patients who received above 625 µg vitamin D_2: 0·75 (0·5) and 6·5 (2·8) nmol/l respectively, while normal concentrations were 4·3 (1·3). These reduced $24,25(OH)_2D_3$ concentrations have previously been found in children with uraemia. (Among these patients there were three cases of cystinosis.[3])

Serum 1,25 dihydroxy vitamin D_3 ($1,25(OH)_2D_3$) concentration depended upon the therapeutic agent used in patients. On either low or high vitamin D supplementation, $1,25(OH)_2D_3$ was below the normal concentrations (25(20) and 5(20) compared with 108(30)pmol/l). Treatment with calcitriol and dihydrotachysterol significantly increased $1,25(OH)_2D_3$ above normal concentrations 190(40) and 900(513) compared with 108(30)pmol/l.

The conclusion of our report[2] on cystinotic patients was in accord with that of Chesney *et al*[3] that circulating values of $24,25(OH)_2D_3$ were reduced in relation to the renal parenchymal damage. The low $1,25(OH)_2D_3$ concentrations could reflect (as also stated by Katzir *et al*) a renal phosphate leak with impairment of synthesis of $1,25(OH)_2D_3$ besides its correlation with renal insufficiency associated with intrarenal cystine accumulation

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Atopic eczema and preterm birth

Sir,

We noted with great interest the report stating that preterm infants are at decreased risk of suffering from atopic eczema,[1] and attempted to confirm this finding using data from a well known data source, the Collaborative Perinatal Project. This project was a prospective study of pregnancy and child development that from 1959 to 1966 enrolled approximately 55 000 pregnancies at 12 centres in the United States. The recruitment and follow up procedures have been described [2] [3] When the subjects were 1 year old, study physicians completed a diagnostic summary form that included a code for eczema. Infant gestational age was determined from the date of the mother's last menstrual period. Children whose birth weight was grossly incompatible with their gestational age were eliminated

There were 44 793 children who survived the first year and for whom the presence or absence of eczema was known. Four thousand and eighty nine (9·1%) of these children were born after less than 37 completed weeks' gestation. Eczema was slightly less common among preterm infants· 1·5% of preterms had eczema compared with

1·8% of term infants. The odds ratio for a preterm infant to have eczema was 0·86, and the 95% confidence interval was (0·66 to 1·11). This indicates that preterm infants are at slightly decreased risk of eczema, but that the difference was minimal and not significant. The 95% confidence interval in this analysis excludes 0·56, which is the estimated odds ratio reported by David and Ewing.[1] Adjustment for maternal race and education (a proxy for social class) did not change the odds ratio substantially.

In summary, this analysis of data from the Collaborative Perinatal Project failed to confirm the hypothesis posed by David and Ewing of a decreased risk of atopic eczema among preterm infants followed to 1 year of age

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Silastic catheters for antibiotics in cystic fibrosis

Sir,

We read with interest the paper by Dr Williams and her colleagues, comparing percutaneous silastic catheters with conventional intravenous cannulas for giving antibiotics to patients with cystic fibrosis.[1] We agree and have reported that these catheters are favoured by the patients, last longer, and have fewer complications.[2]

Since 1985 we have been using a modified version of the catheter described by Dr Williams, which does not require threading onto a 25 gauge butterfly needle (Vygon epicutaneous catheter designed for neonatal use). The manufacturers changed the design of the catheter in 1985 after an incident when a line was accidentally cut by the butterfly needle and apparently disappeared into the child (without ill effect) The new catheter is also marked every 5 cm and is radio-opaque so that it is easy to ensure that the whole catheter has been removed at the end of treatment.

Local anaesthetic cream is applied to the site at least one hour before the procedure The catheter is primed with heparinised saline and is flushed one hour after insertion with 2 ml heparinised saline (100 U/ml) We have not found it necessary to administer a continuous infusion of heparinised saline, but merely flush the catheter every four hours. The catheter is covered with a transparent plastic film and a bandage, allowing the patient freedom to play or even go swimming.

The cost of each catheter (£11·84) is negligible in comparison with the total cost of a two week course of antibiotics Many patients have been able to complete their treatment at home, without the inconvenience of returning to the hospital for a conventional cannula to be resited The technique of inserting the catheter has been taught to the house physicians caring for adult cystic fibrosis patients as well as those caring for paediatric patients at this hospital.

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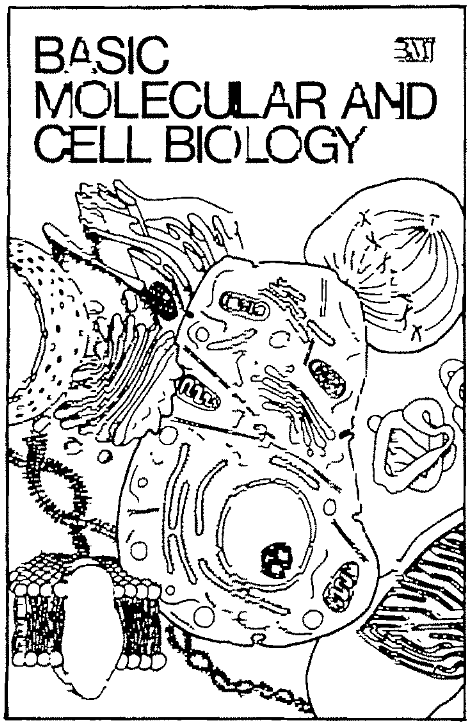

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